L'Institut Servier Annual Scientific Sessions

19th Colloquium 2019
Therapeutic revolutions in oncology:
How to incorporate them?

Phase I clinical trials: new methods

Christophe Massard
Drug Development Department (DITEP), Gustave Roussy Cancer Campus, Villejuif
Molecular Radiotherapy Unit 1030, National Institute of Health and Medical Research (INSERM), Paris
Faculty of Medicine, Paris Saclay University, Paris, France

Springer Healthcare

Abstract

The management of patients with cancer has been revolutionised in the past 5 years by the availability of new treatments known as targeted therapies and immunotherapies. This has become possible thanks to a better understanding of the cancer process. The term "targeted molecular therapy" (TMT) refers to treatments targeting the molecular abnormalities involved in the process of neoplastic transformation. New immunotherapies modulate the immune system to reactivate an anti-cancer response. Fundamental knowledge of molecular biology has altered our view of cancer. A lot of work has also been done to transfer this knowledge from the laboratory to the "patient's bedside". These trials have made it possible to identify the molecular and immunological characteristics of different types of cancers, and shift our thinking away from "organ-specific diseases" (e.g. breast, lung or colon cancer) towards the classification of tumours based on specific molecular abnormalities involved in the cancer process (e.g. HER2-positive breast cancer, EGFR mutations in certain lung cancers, KRAS mutations in colon cancer). This knowledge not only opens the way for a new classification of cancer, but also creates opportunities for new treatments. The methodology used in clinical trials has therefore changed, with the introduction of new trials such as early trials or so-called "basket" trials. Oncology remains an active therapeutic discipline, and medical oncologists are usually less interested in pure knowledge than in knowledge that allows them to come up with new treatment strategies that are increasingly individualised.

NEW TREATMENTS, NEW TARGETS AND A NEW METHODOLOGY

Improvements in our knowledge of the cancer process have led to major changes in the way research is conducted in this area. The methodology of clinical trials in oncology has been shaken up to some extent by the new targets that have been identified in recent years. Molecular screening marks a turning-point, and immunotherapy is a focus of intense research activity.

The way trials are designed is changing rapidly. The traditional paradigm for drug development, consisting of successive phase I, II and III trials, is considered too slow in oncology research since there is an urgent need to make new treatments available for patients. The pattern of development in oncology now consists of a so-called phase I/II study, which incorporates both a phase I and phase II trial within a single study design. The phase I trial explores toxicities and defines the maximum tolerated dose (MTD) in a small population of patients; the phase II trial extends the phase I trial to a larger population. The phase I/II trial is more economical and above all faster than the previous trial process. Some new drugs, such as targeted therapies in enriched populations or immunotherapy with anti-PD-1 agents, are demonstrating efficacy (response rates) in phase I trials, making traditional phase II trials obsolete. Phases I/II trials in oncology therefore define the clinical activity and toxicity of the product, while exploring the biomarkers that indicate activity and response to treatment. A number of drugs have been approved on the basis of phase I/II studies in Europe and by the Food and Drug Administration (FDA) in the United States.[1]

Phase III studies remain essential, since the long-term safety/toxicity of a drug is not well defined in phase I/II trials. In terms of strategy, one important area for consideration concerns phase III trials, particularly platform trials. Unlike basket-type trials that study the safety, efficacy and effects of a single investigational medicinal product (IMP) or a combination of IMPs in a variety of populations, and umbrella-type trials that study multiple IMPs in the same population, platform-type trials can test multiple IMPs in one or more populations, using a complex and highly dynamic design.[2] The platform trial, which is commonly used in oncology research, is useful because it is the best way of defining strategies when phase I trials cannot determine whether the IMP being used is superior to standard treatment.

IMMUNOTHERAPIES AND TARGETED THERAPIES

Immunotherapy has promising and diverse potential, but it is particularly complex. An intense research process takes place to determine how to develop these drugs, which have few or no side effects and sometimes have specific mechanisms of action. The mechanisms of action and pharmacokinetic-pharmacodynamic effects of immunotherapy have justified changes in design and the shift towards the new phase I/II paradigm, in which the trials often have no clear clinical selection criteria. In immunotherapy, there are currently a very wide range of completely agnostic studies (the essence of phase I). Whoever the patient and whatever their cancer is, a phase I treatment appears to be possible, with benefits for many patients thanks to the extremely promising levels of antitumour activity of these agents.[1]

During the next decade, more than 900 new targeted therapies or immunotherapy drugs should be in clinical trials, most of them early phase I/II, for a total of more than 5900 clinical trials. It should be noted that more than 43% of applications for FDA approval are for oncology products. The new paradigm makes it possible to maximise the use of resources in terms of patients, financing and time, while also minimising difficulties for patients, and is likely to speed up the approval process for new therapies, making them available more quickly. Such processes allowed the approval of some agents based on phase I results, including pembrolizumab (studied in 1137 patients) and crizotinib (550 patients) more than 10 years ago, and ceritinib (304 patients) in 2014.[1] This process facilitates rapid access to innovative drugs and is useful for both pharmaceutical manufacturers and academics, but above all for patients.

Today, the era of phase I trials in oncology involving small samples of non-selected patients appears to be over; new, powerful and promising therapies provide justification for large phase I trials recruiting hundreds if not thousands of patients.[1] Numerous targeted therapies and immunotherapies are currently in phase I trials. Carrying out a pre-selection stage or identifying patients to "feed" a phase I trial is a process which, although attractive to manufacturers, is doomed to failure in practice, because it requires considerable effort to screen and select patients with the type of cancer being researched. Experience has shown that thousands of patients would need to be screened because only 1–10% have a tumour with the relevant biomarkers. On the other hand, wide-ranging upstream molecular screening to identify the right study protocol for the patient and their cancer type, is more attractive to both patients and researchers. France, where systematic screening has been taking place for more than 10 years, is doing particularly well in this area.

PHASE I TRIALS IN 2019: INNOVATION AND PRECISION MEDICINE

Experience in oncology research has shown that a major innovation often overturns standard clinical research practice, particularly in phase I trials, and that the availability of an upstream infrastructure provides a competitive advantage for those involved in phase I trials.

Intensification and extension

The Gustave Roussy Institute in Villejuif is following up a large number of patients with various types of cancer, a large proportion of whom (about 25% of patients) have haematological cancers. These researchers have adopted new methods from precision medicine or molecular medicine, leading to a change in traditional phase I trials and utterly transforming phase II trials. The change in methodology involves dose escalation in patients with or without a molecular abnormality. This dose escalation phase is followed by an extension phase involving several hundred patients with molecular abnormalities and very specific tumours.

ESCAT and actionable targets

The European Society for Medical Oncology (ESMO) has recently proposed a classification of "actionable abnormalities", known as ESCAT (ESMO Scale for Clinical Actionability of molecular Targets) in order to promote the implementation of precision medicine in molecular multidisciplinary consultations and in the clinical management of cancer, through the use of a common language for reporting clinically relevant genomic data.[3] The term "actionability" refers to the likelihood that a specific abnormality will constitute a target for treatment (targeted therapy). The ESCAT scale makes it possible to create a hierarchy of cancer mutation markers for selecting patients eligible for targeted therapies, based on clinical evidence supporting the usefulness of these abnormalities as targets for treatment.[3] This classification system defines six levels of clinical evidence, based on the implications for patient management:

- Level I: targets ready for integration into routine clinical decisions
- Level II: experimental targets that are likely to define a population of patients who may benefit from a targeted therapy, but more data are needed
- Level III: clinical benefit previously shown in other types of cancer or for similar molecular targets
- Level IV: preclinical evidence of actionability
- Level V: evidence to justify co-targeting approaches
- Level X: no evidence or insufficient evidence of actionability

Lung cancer is an example of a tumour with targets that are ready to be integrated into routine clinical decisions; testing and treatment of tumours harbouring *EGFRm*, *T790M*, *ALKr*, *ROS1*, *BRAFm* or *METm* should be considered the standard of care. From phases I/II onwards, some treatments have received approval based on response rates of 50% or 80%, demonstrating that it is not necessary to conduct a randomised phase III trial. On the other hand, when the aim is to demonstrate the superiority of a treatment, the traditional (randomised) approach remains valid.

Molecular screening

The French network, with its INCa-CLIP system (centres designated by the Institut National du Cancer [INCa] as early phase clinical trial centres), has given France a significant competitive advantage internationally, particularly in thoracic oncology. After systematic genetic screening over several years, including for the *KRAS* gene, INCa now has some quite large panels of genes. This molecular screening, which is carried out upstream and outside the clinical trial, makes it possible to identify patients who may benefit from participating in specific clinical trials based on the type of cancer they have.

An innovation: *KRAS* inhibitors

The availability of specific drugs targeting mutations of the *KRAS G12C* gene is a first in thoracic oncology. A phase I study has evaluated the safety, tolerability, pharmacokinetics and efficacy of a *KRAS* inhibitor (AMG 510) in patients with advanced solid tumours who have a mutation in the *KRAS G12C* gene.[4,5] This mutation is not common, but it is mostly found in primitive bronchial adenocarcinomas and colorectal cancers. Development of this first *KRAS* inhibitor is progressing rapidly, and phase II studies began only 12 months after the very first administration of the drug in phase I. Interesting response rates have been observed in patients with several types of tumours who have received multiple prior treatments. The duration of response in patients with non-small-cell lung cancer has been prolonged (25–35 weeks).[5]

The potential of complex study designs

Complex study designs allow testing of not only the IMP but combinations or non-standard treatments. Thus, radiotherapy, which it is not possible to dedicate a phase I trial to, can be integrated into the extension phase, as can be done with other forms of treatment. Likewise, and according to the same principle of extension, testing is also possible for "orphan" haematological diseases. In fact, haematology has been integrated into the Service des Innovations Thérapeutiques et Essais Précoces (SITEP; Innovative Therapeutics and Early Phase Clinical Trials Unit) because some patients probably have a haematological condition as the "real" underlying cancer rather than a solid tumour. The best example of this is the significant role of epigenetics in the various types of lymphoma.[6] Epigenetics studies the complex mechanisms that modify gene expression,[7] but we do not yet know how to develop epigenetics or which methodology to follow: combined or sequential?[8] Inhibitors of *HDAC*, *EZH2*, *BET*, *PRMT5* and *IDH* have very specific activity in lymphomas. It is essential to include in phase I trials patients whose tumours have surrogate markers for these diseases, and not to make the mistake of excluding patients with a haematological disease such as a lymphoma, myeloma or acute leukaemia.

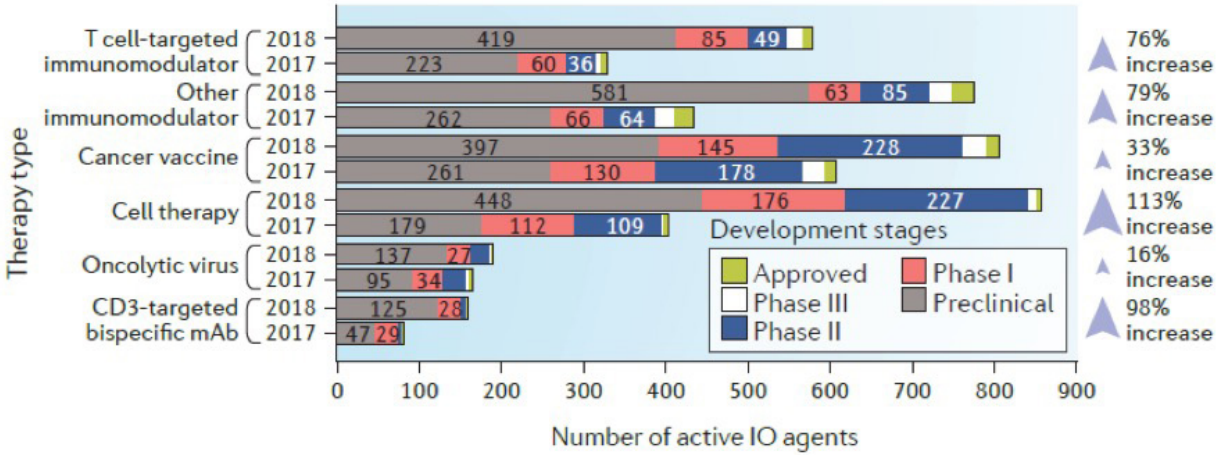
CHANGES IN TRIAL DESIGN IN PHASE I IMMUNOTHERAPY TRIALS

Immunotherapy has revolutionised traditional phase I clinical trial design of dose escalation/extension because these agents have a low level of toxicity and the MTD may only be reached after 6 or 9 months, depending on the way in which toxicity is evaluated. It is also possible to design extensions with different types of cohorts to investigate efficacy in different types of cancer.

Ten years ago, the Targeted Anticancer Therapies group[9] defined a set of rules for phase I clinical trials. In addition to its recommendations on the conduct of phase I trials in immunotherapy, this group raised a number of methodological questions, particularly on the combination of programmed cell death protein-1 (PD-1) / programmed death ligand-1 (PDL-1), focused on reducing redundancy. Tang et al[10] showed that an evolution is taking place in the world of immunotherapy, with investment by an unprecedented number of research organisations and companies. Progress in immuno-oncology in recent years, with the development of combinations of immune checkpoint inhibitors or anti-PD-1 plus chemotherapy, is leading to changes in the standard of care for several types of cancer, and in many cases rewriting the paradigm for treatment and drug development in cancer.[10] The number of active trials using a combination strategy increased considerably over 17 months (from 2017 to 2019), with 835 new studies testing more than 100 additional targets.[10] Nevertheless, the num-

ber of combinations is now reaching a plateau and cell therapies are showing the greatest growth in phase I research (113%) (**Figure 1**).[11]

Figure 1. Trends in immunotherapy research worldwide. 3394 active treatments were identified in six main classes in September 2018, which represents a 67% increase on the previous evaluation.
Reproduced by permission from Springer Nature: Reference [11] Nat Rev Drug Discovery 2018;17:783-4. Tang et al. Trends in the global immuno-oncology landscape. © 2018.



Antibody-drug conjugates (ADCs; monoclonal antibodies conjugated to a cytotoxic agent), such as T-DM1[12] or DS-8201a,[13] are prodrugs designed to improve the therapeutic index by delivering useful anti-cancer payloads to the targeted cells. These drugs have a role in cancers with over-expression of targets such as HER2[12,13] or CEACAM5,[14] whether or not the target is associated with carcinogenesis. New phase I trials are underway with these agents, and report an interesting level of antitumour activity.

CONCLUSION

In oncology, study design from phase I trials onwards is influenced by our understanding of both the cause and the disease, as well as the mechanism of action of drugs. Phase II trials and molecular screening have fundamentally changed the way both basket-type and other trials are conducted. Immunotherapy has been a real revolution for certain cancers and chemotherapy is making a comeback, with ADCs now arriving as a new option. However, the main lesson to be learned from oncology research is that our principal need is not patients for clinical trials but rather clinical trials for patients, and this need can best be met by pre-screening.

REFERENCES (Underlined references link to PubMed abstracts)

[1] Postel-Vinay S, Soria JC. Phase I trials in oncology: a new era has started. Ann Oncol 2015; 26:7-9.
[2] Clinical Trials Facilitation and Coordination Group (CTFG). Available on https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/clinical-trials/clinical-trials-on-medicinal-products/komplexe_klinische_studien.html. Accessed 2019-12-17.
[3] Mateo J, Chakravarty D, Dienstmann R, Jezdic S, Gonzalez-Perez A, Lopez-Bigas N, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2018; 29:1895-1902.
[4] Canon J, Rex K, Saiki AY, Mohr C, Cooke K, Bagal D, et al. The clinical KRAS (G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature 2019; 575:217-223.
[5] Govindan R, Fakih MG, Price TJ, Falchook GS, Desai J, Kuo JC, et al. Phase 1 Study of AMG 510, a Novel KRASG12C Inhibitor, in Advanced Solid Tumors With KRAS p. G12C Mutation. Oral presentation at ESMO 2019.
[6] Sermer D, Pasqualucci L, Wendel HG, Melnick A, Younes A. Emerging epigenetic-modulating therapies in lymphoma. Nat Rev Clin Oncol 2019; 16:494-507.
[7] Arrowsmith CH, Bountra C, Fish PV, Lee K, Schapira M. Epigenetic protein families: a new frontier for drug discovery. Nat Rev Drug Discov 2012; 11:384-400.
[8] Mohammad HP, Barbash O, Creasy CL. Targeting epigenetic modifications in cancer therapy: erasing the roadmap to cancer. Nat Med 2019; 25:403-418.
[9] Seymour L, et al. MDICT Report. https://oncologypro.esmo.org/Meeting-Resources/TAT-2018-Targeted-Anticancer-Therapies/MDICT-report.
[10] Tang J, ShalabiM, Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. Ann Oncol 2018; 29:84-91.
[11] Tang J, Pearce L, O'Donnell-Tormey J, Hubbard-Lucey VM. Trends in the global immuno-oncology landscape. Nat Rev Drug Discov 2018; 17:783-784.
[12] Peters S, Stahel R, Bubendorf L, Bonomi P, Villegas A, Kowalski DM, et al. Trastuzumab Emtansine (T-DM1) in Patients with Previously Treated HER2-Overexpressing Metastatic Non-Small Cell Lung Cancer: Efficacy, Safety, and Biomarkers. Clin Cancer Res 2019; 25:64-72.
[13] Tsurutani J, Park H, Doi T, Modi S, Takahashi S, Nakagawa K. Updated Results of Phase 1 Study of DS-8201a in HER2-Expressing or eMutated Advanced Non-Small-Cell Lung Cancer. J Thor Oncol 2018; 13: OA02.07.
[14] Decary S, Berne PF, Nicolazzi C, Lefebvre AM, Dabdoubi T, Cameron B, et al. A novel anti-CEACAM5 maytansinoid-antibody-drug conjugate for the treatment of colorectal, lung and gastric tumors. Proceedings AACR 106th Annual Meeting 2015; Abstract 1688.