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Revolutions in cancer treatment:
how can they be integrated?

Methods and perspectives

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Abstract

Current clinical practice is built on the foundation of evidence-based medicine. This means that the best available data must be used conscientiously when making decisions. These data are based on clinical trials, so the methodology used in these studies must be well understood. The classic multi-phase pattern of drug development includes a preclinical evaluation, followed by four phases of clinical evaluation (phase I to phase IV). Although this method of drug development is still commonly used, a number of questions arise in oncology. Through the development of recent drugs such as targeted therapies and then immunotherapy, it has become clear that this linear pattern of development cannot be used in some situations. This transformation in the methodology for clinical trials affects early phase I and phase II trials (randomised phase II trials), as well as phase III trials. This roundtable discussion and the presentations by the speakers describe the prospects that may be emerging from these next-generation clinical trials.

INTRODUCTION

Oncology has been a particularly active field of research for a number of years now, particularly in terms of phase I clinical trials. More and more of these phase I studies are taking place, some have been completed and others are in progress, sometimes involving very large numbers of patients. The most common cancer sites being studied are the prostate, lung, breast and kidney; there are also numerous studies looking at colorectal cancer and hepatocellular carcinoma. The changes that can be seen in the history of this research over time are linked to the therapeutic innovations that have become available in recent years.

THE HISTORY OF DRUG RESEARCH

As early as the 11th century, Avicenna took the first steps towards research into treatments, establishing the foundations for the future. From his work, we have inherited a series of principles concerning drugs under investigation. The experiment should be carried out on the human body, the drug should be pure and it should have no external accidental characteristics. It should be used in a simple disease, not a complex disorder, and it should be tested in two different types of disease, since a medicine sometimes cures a patient due to its essential qualities and sometimes the cure is accidental. The quality and strength of the drug should be suited to the severity of the disease. Avicenna also insisted on respecting the time required for a drug to act. Modern pharmacology research has adopted this concept by taking into account the pharmacokinetics of a product and ensuring that the drug is given time to act. He also stated that its effect should be permanent or observed in a large number of cases to exclude the possibility of an accidental effect due to chance. This principle is particularly relevant in oncology when considering the long-term effects of the product and outcomes such as recurrence or treatment resistance.

It is also interesting to consider a number of trials of different treatments carried out in history, such as the one performed by James Lind in 1757 on the effect of vitamin C in scurvy. Lind assigned 12 sailors with scurvy into six groups of two and the patients were given cider (group 1), sulphuric acid (group 2), vinegar (group 3), a concoction of herbs and spices (group 4), sea water (group 5) or oranges and lemons (group 6). Only the last group recovered quickly. The simple methodology used in this trial established the foundations of the modern randomised trial.

INNOVATION IN DEVELOPMENT PATTERNS

The normal structure of drug development involves four phases, each of which has a specific goal:
- Phase I evaluates the tolerability of a product in small groups of subjects;
- Phase II uses the information from phase I to determine the optimum dose;
- Phase III compares the product's efficacy against a placebo or reference product; and
- Phase IV observes the long-term effects of the drug.

Today, changes in phase I trials suggest a need to reconsider this traditional process.

The recent development of extension cohorts makes it possible to go from small numbers of patients to larger groups even during phase I, as in the KEYNOTE 001 immunotherapy trial, in which the initial patient group (n=30) was extended to a population of 1235 patients including extension cohorts.[1-3] Extension makes it possible, for example, to observe that certain populations of patients respond better than others, a process that runs counter to the traditional development model.

Another historical strategy used with some immunotherapies is to investigate the treatment as third line in patients whose disease is incurable. Depending on their efficacy, the treatment may then be tried as second-line and then first-line therapy, and finally, if the drug has proven to be effective in these settings, to test it as adjuvant therapy. While some drugs (such as oxaliplatin, 5-fluorouracil [5-FU], gemcitabine, taxanes and trastuzumab) have shown some efficacy as adjuvant therapy, others have not including irinotecan, which is effective in metastatic gastrointestinal

cancer, and bevacizumab, which is effective as a targeted therapy. These observations suggest that phase I trials should not necessarily be taking place in situations where a treatment impasse has been reached, but should rather be tested at an earlier stage using biomarkers.

EARLY-PHASE INNOVATIONS

The long-held dogma has been that the higher the dose, the greater both the efficacy and the toxicity. This has not, however, been found to be true in every situation, particularly with the latest drugs, antibodies, immunotherapies, tyrosine kinase inhibitors or targeted therapies. Increasing the dose does not always lead to improvements in efficacy and, in many cases, a plateau is reached. An excessive increase in the dose may also turn out to be harmful, due to toxicity.

INNOVATIONS IN EVALUATING TOLERABILITY

The toxicity data from phase I to phase IV reported in the literature are quite limited. A few years ago toxicities of all grades, including grades 1 and 2, or toxicities per cycle were reported. In some publications by originators of phase III trials, a table summarised the proportion of toxicities for all grades combined and for each grade separately. More recent publications have mainly focused on grade 3 and 4 toxicities, and have reported little information on grade 2 toxicities. Despite the incidence of early grade 4 toxicity, which may sometimes go unnoticed clinically or may subsequently diminish – particularly for haematological events – patients may experience a decline in their quality of life due to chronic grade 2 toxicity, which negatively impacts the patient's experience over a number of months.

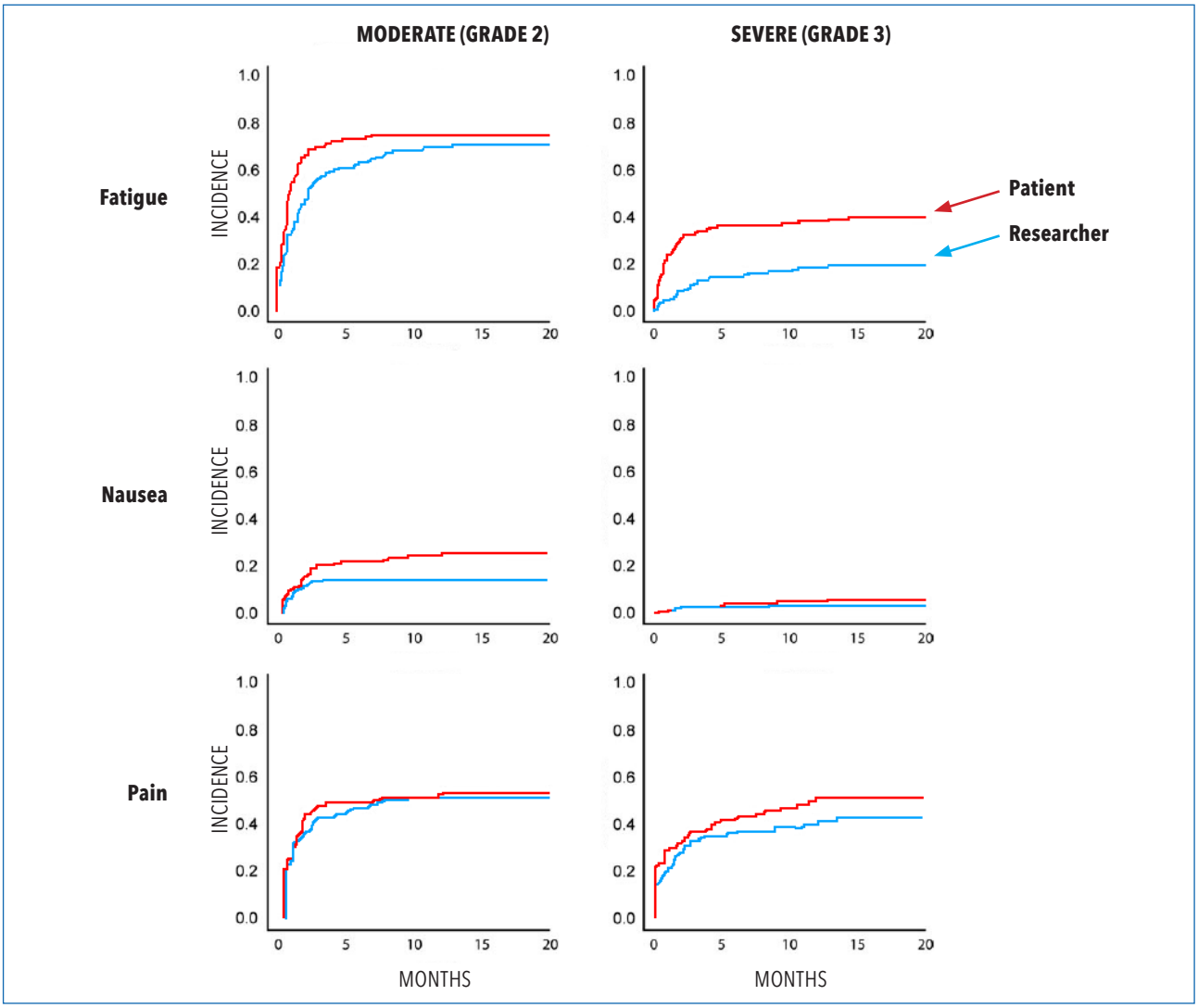
In fact, the reports of toxicity in the literature rarely describe the effects over time, with only acute, medium or late toxicities being cited in accordance with the system of Common Terminology Criteria for Adverse Events (CTCAE) grades. A team of haematologists from the Mayo Clinic evaluated two types of chemotherapy, FOLFOX (folinic acid + 5-FU + oxaliplatin) and IROX (irinotecan + oxaliplatin), and observed different toxicity profiles in different cycles.[4] These profiles were found to differ widely: toxicities were relatively moderate initially and gradually increased during FOLFOX, while on IROX there was a tendency towards a reduction in toxicities.[4] Similarly, the literature does not provide data on long-term adverse effects.

Data on patient-reported outcomes (PROs), a measure of how patients themselves feel about the effects of their treatment, are also rarely reported. This raises the question of how evaluations by the oncologist compare with the patient's own evaluation. According to Ethan Basch et al,[5] when toxicity gradings by patients and researchers are compared, patients are in fact better evaluators than researchers (**Figure 1**).[5] According to these authors, clinicians' CTCAE evaluations, collected longitudinally, provide better predictions of adverse clinical events, while patient reports give a better reflection of their state of health in everyday life.[5]

The lack of adequate toxicity information in the literature suggests a need to improve the way toxicity is evaluated. One improvement would be to differentiate between early and late adverse effects and between acute and chronic toxicities. Taking PROs into account when evaluating toxicity is a concept that is gradually being introduced in evaluations. As suggested by Basch et al,[5] clinician and patient evaluations are complementary since each provides clinically significant information. This justifies collecting both types of data during therapeutic trials.

Fig. 1. Cumulative incidence of symptoms as reported by patients versus clinicians, by month of follow-up. Grade 2 (moderate) or 3 (severe) symptoms based on the CTCAE classification, version 3.0.[5]

Adapted from reference [5], Basch et al, Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst. 2009;101:1624-32, by permission of Oxford University Press.



INFORMED CONSENT

This procedure, which involves ensuring that consent is clear, genuine, appropriate and comprehensible, complies with the rules of Good Clinical Practice (GCP) according to the standards of the International Council for Harmonisation – Good Clinical Practice E6. Although it is vital to apply this GCP rule, we cannot be certain that this procedure is effective or that patients are correctly "informed". In fact, consent forms are long and complex and contain a large number of abbreviations, as well as a lot of unnecessary information, contradictions and details that may even be frightening for patients. It is now known that about 40% of patients do not understand consent forms. The Analysis and Research in CAncers of the Digestive system (ARCAD) Foundation has published proposals to improve and simplify informed consent forms in gastrointestinal cancers (3–5 pages, 1200–1800 words),[6] to provide greater assurance that patients give truly informed consent. Implementation of these proposals will require the support of everyone in the profession.

OTHER AREAS WHERE IMPROVEMENT IS NEEDED...

Further improvements are vital to make oncology research in France competitive with the research conducted in other countries. These include:

- Speeding up the time taken to obtain approval for trials;
- Problems with delays and the competence of Medical Ethics Committees (in France: CPPs), whose membership is determined at random, leading to risks that the committee may not really understand oncology or the complexity of certain trials;
- The criteria for membership of a Data Safety and Monitoring Board;
- In phase III trials, the ethical principle of clinical equipoise, i.e. that the two treatments in a randomised trial should be relatively balanced. This principle raises ethical questions on randomising patients to a treatment with known efficacy and a standard that is not very effective or outdated; and
- The need for clinical trials to be environmentally economical in terms of carbon accounting.

CONCLUSION

Oncology research carries some inherent challenges that call into question the traditional pattern of drug development, although this pattern is still often used. Innovation and improvement are needed in a number of areas affecting both the methodology used in clinical trials of next-generation therapies and the national procedures for the conduct of these trials.

REFERENCES (Underlined references link to PubMed abstracts)

[1] Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Elassaiss-Schaap J, Beeram M, et al. Phase I Study of Pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors. Clin Cancer Res. 2015;21(19):4286-93.
[2] Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013;369:134-44.
[3] Khoja L, Butler MO, Kang SP, Ebbinghaus S, Joshua AM. Pembrolizumab. J ImmunoTher Cancer 2015;3:36
[4] Thanarajasingam G, Atherton PJ, Novotny PJ, Loprinzi CL, Sloan JA, Grothey A. Longitudinal adverse event assessment in oncology clinical trials: the Toxicity over Time (ToxT) analysis of Alliance trials NCCTG N9741 and 979254. Lancet Oncol. 2016;17:663-70.
[5] Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst. 2009;101:1624-32.
[6] Bleiberg H, Decoster G, de Gramont A, Rougier P, Sobrero A, Benson A, et al. A need to simplify informed consent documents in cancer clinical trials. A position paper of the ARCAD Group. Ann Oncol. 2017;28: 922-930.