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Abstract
The paper reviews some of the transformations of cancer clinical trial protocols made necessary by the emergence of molecularly targeted agents. These changes include the creation of a new phase of clinical trials (phase 0) and the alteration of the parameters governing the other three phases. The situation remains unstable: repeated attempts to speed up the development of new drugs have not yet led to a consensus on how to best do so. The new targeted agents raise issues that go beyond the purely technical as changing protocols implicate changes in the organization of translational research.

Keywords
Cancer clinical trials • Targeted drugs • Clinical trial design • Oncology • Personalized medicine

Introduction

Mention of personalized medicine in oncology immediately evokes two different kinds of clinical trials: those designed to validate prognostic or predictive biomarkers, and those designed to test new molecularly targeted agents (MTAs). The first category includes clinical trials such as TAILORx (in North America) and MINDACT (in Europe) that seek to establish the clinical relevance of breast cancer genomic signatures, rather than to test a particular drug or drug combination, as in more traditional trials [1]. These "proof of concept" trials seek to adapt the clinical trial methodology developed in chemotherapy to molecular diagnostics with the ultimate goal of predicting whether individual patients will derive benefits from chemotherapy and, if not, sparing them unnecessary treatment. The second category deploys many of the traditional components of chemotherapy trials, but the advent of MTAs has made adjustments necessary. Companion diagnostic tests, i.e. those designed to detect the molecular targets of MTAs and thus to decide whether a specific drug will work in a particular patient [2], act as bridge between the two categories. Both categories raise important organizational and regulatory issues, as they imply new modes of interaction between pharmaceutical companies, academic and public clinical institutions, cancer agencies, regulatory bodies, professional segments within the field of oncology, and patient groups [1]. This paper will focus on the redesign of clinical trials to adapt them to MTAs.

The targets of the MTAs are those provided by molecular biology [3]. The novelty of targeted medicine is not that MTAs have targets — older agents also had them — but that the targets are more recent (cell signaling molecules, oncogenes, cell cycle regulation proteins), they are often better characterized in molecular terms, and the agents directed against them are numerous: more than 900 anticancer drugs and vaccines are currently under clinical investigation, a 150% rise over the year 2000 [4]. This dramatic increase can be accounted for by the fact that while oncology was traditionally a largely academic undertaking, pharmaceutical companies have made massive investments in the domain since the mid-1980s; once a relatively marginal field, cancer has become a major pharmaceutical market [5]. The number and kind of new agents that have emerged in the course of the last 15 years — often aiming at similar targets and thus acting as

direct substitutes for existing products [6] — has raised several problems that necessitate a redesign of cancer clinical trials [7]. These problems present themselves at all phases of clinical cancer research and have, in fact, led to the creation of a new phase of clinical trials, phase 0.

MTAs create three kinds of problems for clinical trials that, if not solved at one level of the process, resurface at the next. First: in phase I trials, toxicity is not necessarily an appropriate means of measuring dose size as in the case of cytotoxic agents. Second: phase II trials normally measure variables such as tumor regression following standard criteria, e.g. the RECIST criteria assembled at the beginning of the new century by representatives of the European Organization for Research and Treatment of Cancer, the National Cancer Institute of the United States, and the National Cancer Institute of Canada [8]. If a cytostatic agent merely stops growth without killing cells, then tumor regression is not necessarily a useful endpoint for phase II trials of such agents. Third: given their mechanism of action, the large number of new MTAs and the fact that some of them target more than one pathway, there may simply not be enough time to evaluate all the possible combinations of patients and drugs in phase III trials according to the old system that ultimately required thousands of patients, hundreds of millions of dollars and a decade of research per drug [9]. The complexity of the phase III process cannot be underestimated. Experts in operations management have calculated that it takes approximately 810 steps to open a phase III trial implicating as many as 38 different individuals and groups in the decision-making process [10]. It is thus little wonder that 64% of all phase III cancer trials sponsored by the NCI between 2000 and 2007 failed to meet their minimum accruals [11]. In addition to an increase in drug development time, and although estimates of the cost of developing new drugs vary — they range from $500 million to $2 billion per successful launch [12] — the cost of pursuing clinical trials has significantly increased, while their success rate has decreased [13-14].

As a result of these different factors, since the middle of the last decade the entire system has been pervaded by a sense of crisis that in April 2010 culminated in the release of an Institute of Medicine report that recommended improvements in the speed and efficiency of trials, the incorporation of innovative science and trial design, improvements in the prioritization, selection and completion of trials, and more incentives to enroll more patients and physicians in the trials [15]. These epistemic and logistic problems have prompted numerous other initiatives to speed drugs through the phase 0-III process and to reduce failure at all levels. In 2000, for example, the NCI developed a grant program to develop ways to assess novel clinical trial endpoints [16] and in 2002, the members of EORTC's New Drug Development Program called for new forms of clinical trials — new study templates with redesigned study statistics and study performance — in order to deal with the new types of compounds emerging from the study of molecular targets [17]. Our purpose here is to give the reader a general sense of how MTAs have changed clinical trial protocols, beginning with the most striking reform: the creation of an entirely new phase of clinical trials known as phase 0.

Phase 0 trials

In 2006 the FDA issued a Guidance document that introduced the notion of phase 0 trials, also known as micro-dosing studies [18]. The purpose of this new category of trials is to administer sub-therapeutic doses of an experimental drug to gather data on its behavior in the human body, and in particular to assess whether the drug has an impact on its intended molecular target. The avowed goal is to speed up drug evaluation by largely avoiding the scaling-up process (the

amount of drug needed for the trial could be supplied by laboratory procedures) and by skipping the human toxicity stage through the use of sub-clinical doses while reducing the danger of adverse reactions, thus eliminating a number of toxicity studies in animals. Subsequent studies claimed that the time saved ranges from 3 months to a year [19].

The FDA Guidance did not set out precise rules on how to proceed with phase 0 trials. Instead, it offered three examples of what a phase 0 trial might look like and invited investigators to experiment with the paradigm outlined by the three exemplars and to devise, in concert with the FDA, similar trials. The examples included in the Guidance came from a mix of public and private sources: the NCI, the European Medicines Agency, and the Pharmaceutical Research and Manufacturers of America (PhRMA). Pharmaceutical companies have responded favorably: in addition to praising the flexible nature of the new phase concept, in the three years following the issue of the Guidance they conducted more than 23 expIND (phase 0) trials [20]. A review of those trials concluded that "without exception, subjects participating in these trials [had] not been compromised in any manner" and that "in each case, the corporate objectives [had] been achieved through huge savings in the synthesis of materials, huge savings in non-rodent animals, and huge savings in time intervals to first-in-human dosing" [20].

Not all reviews have been positive. While phase 0 trials seem to eliminate steps in the drug development process, they ultimately add a step. As Richard Schilsky, the Chairman of the cooperative oncology group CALGB pointed out at a workshop on phase 0 trials, "at the end of the day, if you're going to bring your drug through the full clinical development plan, you're still going to need the full package of data", and thus phase 0 was "not a shortcut" [19]. Phase 0 trials also raised vexing questions for patient. Since the drugs tested would all be tested at doses well below the level of clinical effects, such trials would clearly have no therapeutic intent. What then would motivate patients to enroll in a phase 0 trial? While altruism might seem to be the obvious answer, the era of patient activism offered another. According to Deborah Collyar, founder of patient advocacy in CALGB and president of "Patient Advocates in Research", phase 0 trials would allow patients "to act as participants instead of research subjects" and consequently "help improve how some drugs can be evaluated" [21].

Phase 0 trials are not, however, without risk for participants. In addition to the relatively small risk posed by repeated tumor biopsies, a much larger issue concerns the ability of patients to understand that no therapeutic intent really does mean what it says. Clinical cancer trialists know from experience with phase I trials that even though the latter also have no therapeutic intent, patients enrolled in the trials often believe that there is a possibility that their cancer may be alleviated if not cured [22]. In order to avoid confusion, the NCI Ethics Committee that reviewed the phase 0 protocol for a novel PARP-inhibitor insisted that the patient consent forms contain the following statement: "This clinical study does not intend to treat your cancer". Patients who agreed to enter the trial were then obliged to sign a document that stated: "I understand that participating in this study will be of no therapeutic benefit to me but may be of benefit to others" [21]. In addition, by participating in the study patients also deprived themselves of the opportunity of participating in concurrent and, depending on the kind of intervention, future trials. The forms thus further notified participants that: "Your participation in this study may delay … or exclude your ability to participate in other clinical trials" [21].

Despite the initial enthusiasm, the future of phase 0 trials remains uncertain. An independent international task force concluded that while the idea is promising, the extent to which phase 0 trials will reduce drug development times and attract patients can only be decided on the ground and thus proposed that phase I and phase 0 trials be run "in parallel in order to evaluate the impact of the phase 0 trial on the subsequent development of an agent" [23], thus submitting the new phase concept to a sort of clinical test.

Phase I trials

When testing cytotoxic substances, phase I trials often use toxicity as a surrogate for setting effective dose levels. Numerous trial designs exist for the estimation of this parameter including the most common 3 + 3 cohort expansion design that expands an initial cohort of 3 patients by groups of 3 until a toxicity rate of 33% is achieved [24]. With molecularly targeted agents, there is often no correlation between toxicity and clinical effect [25]. Thus, alternative endpoints must be used to determine effective dose levels, such as measures of target inhibition and the measurement of blood levels of the agent under study [26]. More than simple endpoint changes, such studies require significantly closer contact between the laboratory and the clinic and add considerable expense to the phase I trials [27]. Indeed, studies have shown that the research infrastructure needed to conduct phase I trials is now significantly greater than that needed for phase II trials. Using surrogate markers also restricts patients to those that express the marker in question even though such limitations further reduce stressed patient pools [28]. This may in part account for the widely decried fact that academic oncologists are "losing control" over phase I trials [29].

While it remains true that the goal of Phase I is not to test for efficacy, and while it is indeed possible that the target of a drug will turn out to be different from the one initially described, it makes clinical sense to determine the recommended dose of a substance defined by a given target on patients whose tumors have the appropriate profile, rather than on generic cancer patients. This strategy can change the goal of phase I trials of a new drug into one that not only evaluates toxicity but also preliminary evidence of efficacy, thus turning phase I into phase I/II trials. Finding a molecular biomarker that adequately reflects the anti-cancer properties of a targeted drug, however, is not as straightforward as it might appear. Clinically validated biomarkers are rarely available and the penury of adequate markers was confirmed in a review of reports of 60 phase I trials of cytostatic agents targeting solid tumors that appeared between 1998 and 2003. Only one third of the trials used surrogate markers to study drug effects; the other two thirds relied upon traditional measures of toxicity. Of the third that used surrogate measures, only one restricted patient entry for the surrogate. A study of abstracts presented at the ASCO annual meeting from 1991 to 2002 came to a similar conclusion: almost 80% of phase I trials proceeded without biomarkers and used traditional toxicity criteria [30-31].

Using a biomarker to show that a target has been blocked is insufficient from a clinical point of view, as most targeted therapies inhibit but a single step in an extremely complex biochemical pathway [24]. The slow progress in the search for biomarkers for phase I cancer trials has provided fertile ground for skeptics who argue that "the enthusiasm for widespread adoption of biomarker studies in early drug development is unjustified because of statistical and cost considerations, as well as a lack of historic evidence for their usefulness" [32], and dryly note that "despite all major leaps in cellular and molecular biology, there is currently no agent for

which a biomarker has been identified that is known to adequately reflect antitumor activity of that particular agent in humans" [33]. Moreover, and in spite of the preceding remarks, the view that the notion of maximum tolerated dose is irrelevant as concerns MTAs, has yet to garner consensus [33]. Indeed, reviewing pros and cons of using toxicity as a primary phase I endpoint, the NCI's Task Force on Methodology for the Development of Innovative Cancer Therapies concluded that toxicity remains a "reasonable endpoint" for MTAs and that in cases where biomarkers are needed for molecular proof of principle for further development of the agent, investigators should consider simply expanding one of the phase I cohorts for additional investigation [34]. The central question in choosing an endpoint for a phase I trial according to the Task Force is how much investigators "need" to know about agent/target interaction in order to move on and how much knowledge is simply "desirable". Given that the line between the two "may be difficult to judge" [34], it is probably no surprise that the Clinical Trial Design Task Force of the NCI concluded in 2010 that "the design of phase I trials remains an open issue" [24].

Phase II trials

Like phase I trials, phase II trials of targeted therapies raise issues with regards to the endpoints measured and thus to the type of trial conducted. Phase II trials have traditionally used standard measures of tumor reduction in solid tumors or complete remission in leukemia to gauge therapeutic efficacy. Targeted therapies, however, may produce growth delay rather than growth reduction. Moreover, some of the best-known MTAs such as trastuzumab, cetuximab, and bevacizumab, did not work well as single agents and produced few clinical responses in phase II studies [35]. In other words, it may well be the case that most targeted molecules will find their true efficacy as components of a multi-drug regimen rather than as single agents.

As a result, phase II investigators have sought alternative endpoints to test MTAs, such as disease stabilization, time to progression, and progression-free survival. The extent to which these new endpoints, many of which involve the measure of biomarkers, are specific to MTAs has been contested and a survey of phase II trials has found that just as many traditional cytotoxic trials use stable disease as an endpoint as targeted therapy trials [36]. Be that as it may, these time-to-event endpoints are considered a more adequate reflection of the therapeutic benefits of cytostatic agents than more traditional endpoints such as tumor reduction [37]. Researchers have consequently called for "more complex phase II designs with time to progression endpoints" in order to save drugs that show great promise in the laboratory and phase I but fail to show up in traditional phase II trials [35] and thus to screen cytostatic drugs more effectively. Several alternative designs have been proposed [38]. A noteworthy example is the I-SPY-2 neo-adjuvant breast cancer clinical trial: launched by the Biomarkers Consortium — a public-private partnership that includes the FDA, the NIH and a number of pharmaceutical companies — and supported by patient advocates, the trial has enrolled almost 20 major cancer research centers in the US. In addition to using an adaptive (Bayesian) design, it relies on the extensive use of biomarkers to rapidly screen a number of experimental MTAs [39]. The extensive use of biomarkers underlines, once again, the necessity of creating smooth interfaces between the laboratory and the clinic and raises the issue of how these new tools will transform clinical judgment and affect the work and role of (molecular) pathologists [40].

The need for randomization at the new phase II level in trials with MTAs raises unique questions in oncology where, unlike other specialties where randomized phase II trials are the norm, such

trials remain relatively rare [41-43]. Although a review of phase II trial between 1986 and 2002 noted a marked increase in randomized protocols [44], a review of phase II oncology trials published in 1997 revealed that only 4 of 308 trials reported current controls [45]. Similarly, a review of phase II clinical trials published in 2003 showed that less than 10% of phase II trials were randomized [46]. A much smaller study of phase two publications in 2004 culled a much larger percentage: 22% [37]. Nonetheless, overall, and despite the current upward trend, the vast majority of phase II clinical trials remain non-randomized, using historical controls as comparisons.

Questions of trial design, randomization and the use of biomarkers prompted the Investigational Drug Steering Committee of the National Cancer Institute to create a Clinical Trial Design Task Force in 2007. Composed on members of the IDSC and external members from academia and industry, the Task force organized a number of workshops that resulted in the publication of working documents in a special issue of *Clinical Cancer Research* in 2009 and, following review and revision, a "consensus conclusions" in 2010 [47]. Concerning randomization in phase II trials, they concluded that non-randomized designs would be acceptable only in cases of monotherapy trials where the endpoint was tumor regression. All other cases, i.e. those involving combination therapy and/or measures of progression free survival should be randomized. A debate in the *Journal of Clinical Oncology* arrived at a similar consensus statement [48].

The Task Force also recommended against the use of biomarkers to enrich the patient population in phase II trials primarily because so few markers have been validated [47]. They did however recommend using such trials to generate biomarkers for subpopulations that may be especially sensitive to the MTAs under investigation. The disappointing results obtained by gefitinib were a cautionary tale in this regard. While promising results for the compound emerged from phase I and phase II studies, the drug failed to show any advantage in a pivotal phase III trials with patients with refractory advanced non-small cell lung cancer. Subsequent analysis suggested that the drug might have had some success with a selected sub-population [49-50]. In light of this and other well-known phase III failures, the Task Force recommended that investigators consider stratified, adaptive designs that allow phase II trials to select a population in the course of a trial and continue study of the subpopulation in order to provide more precise indications for phase III trials [51-52].

The transition to phase II trials devoted to targeted therapy is not complete as, in addition to the continuing use of historical controls, most phase II trials measure traditional endpoints such as tumor reduction [37]. The persistent use of classical endpoints is not simply a refusal to change. Molecular targets do provoke changes in short-term endpoints and in this sense can be used to select effective agents. The effects observed, however, are generally lower than those observed in cytotoxic chemotherapy [53]. The question then becomes, should researchers proceed to phase III trials based on results obtained in phase II trials that are lower than what has been the norm in the study of cytotoxic drugs [54]? This question is particularly relevant as a recent study shows that the phase II success rates have fallen from 28% to 18% between 2006/2007 and 2008/2009, and that cancer clinical trials accounted for 20% of these failures [55].

Phase III trials

The molecular turn in cancer clinical research has refocused the attention of researchers and investors on Phase I/II trials from which new MTAs are expected to emerge. It has thus upset the balance between these early phases of the drug development cycle, and phase III trials that traditionally compared regimens involving permutations of a relatively small number of agents. As a result, cooperative oncology groups whose main task has until now been to carry out large-scale phase III trials, have reacted to the growing commercial involvement in cancer research by redefining themselves as academic research organizations [56]. Phase III trials remain, nonetheless, the basic requirement for the final approval of a drug by regulatory agencies such as the FDA and EMA. Regulatory agencies, in turn, have adapted regulations to the new complexities of drug development. In May 2002, for instance, the FDA issued a guidance for a procedure known as Special Protocol Assessment (SPA). SPAs allow Phase III trial sponsors to submit a request detailing the trial's design, clinical endpoints and statistical analyses, in order to obtain an agreement from the FDA *before* the completion of the trial (ideally at the end of a Phase II) stipulating that should the trial be executed exactly as planned, and the results be positive, the drug will be approved [57].

The gold standard for a phase III trial remains, of course, survival. While directly measurable in terms of overall survival, this can be a long and costly process. So, as in the revamping of the previous phases, trialists have looked to surrogate measures to reduce costs and to speed up study time [58]. Among the measures known to serve as proxies for overall survival are tumor response, disease control, progression-free survival, and time to progression [59]. Unlike survival, some of these endpoints may suffer local variation in their measurement, a problem that has led to calls for different forms of centralized control and auditing [60-61]. Which of these measures may be a useful surrogate depends in part upon the mechanism of action of a targeted compound. Some compounds, like imatinib, do produce a reduction in gastrointestinal tumors; others reduce tumor size in only a subpopulation of patients, whereas still others simply stabilize the disease [62].

The problem remains that even when overall survival is used as an endpoint, cytostatic therapies do not always measure up. With one exception, all of the large trials of MTAs reported in 2002-2003, for example, failed to show an increase in overall survival. While this may indeed have been proof that the drugs didn't work, there was at least some evidence at the phase II stage that they did, and one cannot exclude that there was possibly a subgroup in those trials that had reacted positively. Consequently, as we have seen in the case of phase II trials, much hope is currently invested in the use of biomarkers to sort through the heterogeneous nature of most cancers in order to select the reactive subgroups that remain hidden in standard trials. Using biomarkers to select and stratify patients will clearly rework the ways in which phase III trials are planned and organized. As NCI's chief biostatistician, Richard Simon, recently remarked, "the basic underpinning of doing broad-based clinical trials and then doing post-hoc subset analyses, but not believing them, no longer really is what we should be doing" [63]. Instead, protocols incorporating biomarkers (or, more generally, companion diagnostics) will build subset analyses into the trial design from the beginning. The biomarkers themselves, however, need to be clinically validated, and this, in turn, requires large randomized clinical trials that raise their own set of design issues. Based on the examination of concrete examples, a recent, detailed review of the statistical and practical advantages and limitations of a number of available designs concluded that in order to assess the clinical utility of a biomarker, clinicians should opt for biomarker-stratified designs, but that implementing such designs requires, in turn, special interim monitoring

rules to maintain a proper balance between scientific considerations and the protection of patient interests [64].

Phase III trials of MTAs do not escape the perennial problem of patient accrual. Even though biomarkers may potentially enrich the reactive population and thus reduce sample size, those bearing the marker in question will still have to be screened. Researchers conducting a recent trial of transtuzumab in HER2 positive patients had to sift through almost 4,000 patients to finally enroll 600 in the trial [65]. When the biomarkers and the biology are not clear, phase III trials become a form of learning by doing through the adoption of adaptive designs. MTAs have thus created interest in the use of novel adaptive designs not only at the phase II level (as exemplified by the aforementioned I-SPY 2 trial) but also at the phase III level. Adaptive designs allow researchers to modify a number of clinical trial parameters in the course of a clinical trial and according to the accumulating data. In the case of phase II trials, those parameters include the number of patients needed to reach a conclusion, the range of doses tested, the types of populations tested and the degree of randomization deployed by the trial. More importantly, if one arm of a comparative trial proves itself to be superior to the other arm, then patients can be reassigned to the superior treatment in the course of the trial.

Conclusion

Clinical cancer trials are currently in a state of flux prompted by the massive movement of molecular biology techniques, targets and agents into the sphere of cancer therapy. While there is consensus on many topics, that consensus is often about the future and does not map easily onto the present. A consistent theme of the past decade has been the need to move drugs and biomarkers more quickly through the drug pipeline. The pipeline, however is more metaphorical than real, insofar as knowledge in the field of cancer does not flow in a unidirectional manner. As we have seen, clinical cancer trials, from phase 0 to phase III are closely interconnected; findings in phase III trials, for instance, can often impact phase II trials in a reversal of the knowledge flow implied by the pipeline metaphor. Innovations at one level have repercussions at all levels. Moreover, adjustments made necessary by the emergence of MTAs are not confined to fixing a few technical parameters, but require a rethinking of both epistemic and organizational issues made necessary by both a transformation of the relations between the traditional players in the oncology domain, and by the emergence of new stakeholders.

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Conflict of interest

The authors declare that they have no conflict of interest

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