Research biopsies in the context of early phase oncology studies: clinical and ethical considerations

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Abstract

The Personalized Medicine approach in oncology is a direct result of an improved understanding of complex tumor biology and advances in diagnostic technologies. In recent years, there has been an increased demand for archival and fresh tumor analysis in early clinical trials to foster proof-of-concept biomarker development, to understand resistance mechanisms, and ultimately to assess biological response. Although phase I studies are aimed at defining drug safety, pharmacokinetics, and to recommend a phase II dose for further testing, there is now increasing evidence of mandatory tumor biopsies even at the earliest dose-finding stages of drug development. The increasing demand for fresh tumor biopsies adds to the complexity of novel phase I studies and results in different challenges, ranging from logistical support to ethical concerns. This paper investigates key issues, including patients' perceptions of research biopsies, the need for accurate informed consent, and alternative strategies that may guide the drug development process.

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Introduction

Oncology drug development is increasingly shifting from a *one size fits all* paradigm towards a personalized, biomarker-driven approach taking intra- and inter-patient tumor heterogeneity into account.[1,2]

Until recently, biomarkers have commonly been identified retrospectively, often after late stage failure of large randomized phase III trials. Well-known examples are the development of the EGFR small molecules, gefitinib and erlotinib, in non-small cell lung cancer where only retrospective analyses identified a subset of patients who gained benefit from these drugs.[3-5] Such an approach may be valid in generating hypotheses; however, a major concern is the underestimation of the *real* treatment benefit for the identified subgroup and exposure of patients to potential side effects.

Incorporating measurement of pathway activity and tumor efficacy into early phase trials may help to avoid failure in later phases of drug development.[6] As a direct consequence, there has been an increased demand for archival and fresh tumor analysis in early clinical trials to foster proof-of-concept biomarker development, to understand resistance mechanisms, and ultimately to assess biological response. Although phase I studies are aimed at defining drug safety, pharmacokinetics and to recommend a phase II dose for further testing, there is now increasing evidence of mandatory tumor biopsies even at the earliest dose-finding stages of drug development.[7] In particular, the increasing demand for fresh tumor biopsies prior to trial enrolment or on study and during progression adds to the complexity of novel phase I studies and results in different challenges ranging from logistical support to ethical concerns.[8-10]

In this article, we review clinical and ethical aspects of tumor biopsies for early clinical trials and the challenges in balancing between *patient benefit versus harm of intervention*.

Patient's perception of tumor biopsies

Patients often participate in phase I studies as they regard this option as an *active* treatment alternative, finding comfort from routine visits to the clinic and diagnostic tests as contributing to a sense of control or hope.[11-14] The concept that patients gain hope in order to *fight* their illness has been well described as a coping strategy, resulting in improvements in patients' Quality of Life, wellbeing and in their participation in treatment regimes. Furthermore, the level of hope and its use as an effective way of coping seems to be universal to various cancer diagnoses, and doctors should always be supportive, in a patient centered manner, albeit while counteracting unrealistic optimism.[15,16]

This group of patients, though not necessarily demographically vul-

nerable,[17] may be particularly *fragile* due to their prognosis and could, therefore, be under a therapeutic misconception.[18-20] It has been suggested that patients extrapolate this misconception about the trial in general to include benefits from research biopsies,[9] not only discounting the potential toxicity of the new drug tested, but also the risks associated with undergoing these biopsies.[9,10,21]

In addition, the patient's acceptance of the risks associated with biopsy has been shown to be higher than those generally accepted by the Research Ethics Committees and investigators themselves, with nearly a quarter of patients saying they were willing to accept a 5-10% risk of a major complication.[8] This may reflect their lack of treatment alternatives; however, it raises questions about how much information patients have regarding the risks associated with research biopsies during the consent process.[9,22,23]

In response to these ethical considerations, reviews of the soundness of the consent process have been undertaken. Motivators such as trust in their doctor, the credentials of an institution, and the internal pressure to *be doing something* should not mask the process of voluntary consent, the understanding of therapeutic benefit (or the lack of it), and the potential risks associated with research procedures.[11]

Ethical considerations concerning biopsy in research and how these are reconciled

One of the ethical challenges of trial participation rests in the discordance in the balance between the risks of the associated procedures and any possible benefit to the patient. The use of biopsy has been questioned as *taking without giving in return*.[24] There is evidence in the literature that there is often no direct benefit from research biopsy for the research participant, and that, indeed, there is a potential for harm. Therefore, consideration has been given to how its use should be justified.[24-27]

Research biopsies should be differentiated according to their primary research purpose.[28] These purposes represent a spectrum of ethical acceptability in the types of tissue biopsies used for research, ranging from those obtained from clinical specimens to those obtained purely for research purposes for correlative science.[29]

Arguably, a proportional spectrum of scientific justification is required for the use of biopsy in each category. It is important that all studies obtaining biopsies should clearly explain the scientific rationale for their use with a statistical plan to highlight how the biopsy will be useful to science.[26,28] However, there will be limits to our ability to justify in advance the use of correlative research biopsies by the likelihood that they will make a vital contribution to answering a particular scientific question.[24] Ultimately, this *vital contribution* may be based on the unknown consequences of refuting the research conjectures, such as gaining information on mechanisms of resistance, understanding why a drug did not hit its intended target, or why when it does the intended response did not occur. This new understanding generates a new hypothesis that promotes advancement within the practice of research.

One proposed solution to both the idea that use of biopsy should be justified and that it may also affect trial enrolment is that its use should be optional rather than mandatory.[24] The argument that it is unethical to deny entry to a trial based on a patient's unwillingness to undergo a mandatory biopsy is also rightly refuted[6,25,26,28] as this wrongly assumes that the denied treatment is effective and such an assumption is contrary to the inherent nature of a trial as a scientific experiment. As such, it has been pointed out that we have a moral obligation to include mandatory correlative research biopsy and maximize the research potential of all trials even when our understanding is so limited.[25,29]

There has been some recognition that mandatory biopsies impact on trial accrual and that, when given the choice, patients opt not to have a biopsy.[8,30] However, if the trial is proposed with a mandatory biopsy, up to 50% said it would not impact their willingness to enter and patients generally accepted the procedures knowing it would benefit the scientific community.[30,31] A further point towards justifying mandatory criteria is that if by giving patients the choice it leads to too few results for statistical power,[24] resulting in a wasted effort on the part of those who do participate.[28]

As the potential scientific benefit is weighed against the lack of direct patient benefit, it is important to consider the potential side effects of additional tumor biopsies. Importantly, results from a 2012 study by Gomez-Roca *et al.*[32] demonstrate that the majority of patients from 14 phase I clinical trials tolerated biopsy procedures well, despite the lack of clinical benefit, and this is in agreement with results from previous studies.[8,30,31] However, it has recently been highlighted that some sites carry significantly more risk than others and that this is not necessarily made clear to patients during the consent process.[9]

Informed consent

Unfortunately, these concepts may not be clear to patients. Data assessing the understanding of patients on the non-beneficial nature of research biopsies suggests a lack of clarity and a need for a more transparent consent process, with a study by Helft and Daugherty showing as many as 42% of participants believed the biopsy would influence their health and care.[24] In addition, a recent analysis of the contents of informed consent forms used in trials requiring biopsies shows that much work has been undertaken to prevent any therapeutic misconception regarding the trial agent but the same efforts have not been made to highlight the research nature and lack of benefit from the biopsies and biomarker studies.[9]

It is, therefore, essential that information regarding both the role of research biopsies and their associated risks, including complications by biopsy site, are made explicit in the consent information.[9,33,34] Methodologies for improving the consent process have been suggested and include recommendations such as developing protocols in consultation with a research ethics committee, using an independent provider to gain consent, distinguishing between consent for agent and consent for biopsy, or even offering a small financial compensation to reinforce the absolute lack of individual medical benefit.[6,35]

Alternative biomarker technology

Finally, it is important to seek less invasive alternatives that can be validated alongside correlative studies of tumor biopsies.[35] This should include work to refine biomarker assays, optimize tissue handling protocols, and obtain reliable, reproducible data before the drug moves on to the next phase. Such assays can study the effect of the drug in the tumor sample and look for associations between the biopsy and surrogate cell markers such as peripheral blood, skin tissues or application of molecular imaging studies to evaluate downstream target effects.[6,36-38] A valid alternative option could be the use of archival tissue. However, this may not be representative of some biomarkers that are closely related to late stage changes (PTEN deletions in colon cancer or c-MET alterations in non-small cell lung cancer). In addition, the quality of sample collection due to tissue preservation and processing could be poor, and this potentially affects the quality of molecular data, limiting

the success of a selected biomarker analyses. On the other hand, archival paraffin-embedded tissues could be the most accessible materials available for analyzing important surrogate markers for therapy, as well as potential surrogate markers at DNA, mRNA and protein levels. Similar ethical considerations to those described above should also be applied to archival tissue, focusing on scientific usage and informed consent, although harm would not be a factor in the future use of samples. Patients surveyed showed a significant degree of acceptance of the idea of using tissue samples for multiple research purposes, when a bioethical assessment of usage has been undertaken.[38]

Circulating tumor DNA and circulating tumor cells are promising intermediate biomarkers already being validated as prognostic markers in patients with metastatic prostate, breast and colorectal cancer. Where there are clear associations and an indication that surrogate tissues reliably predict drug effects in tumor, this will potentially reduce the future need for biopsy and should be a key area for exploration. Guidance is starting to come from international working groups and drug licensing agencies to govern developments in this area.[29,37,39,40]

Also, innovations in how research institutions share data are needed to speed up the development of biomarkers. Early signs of unexpected efficacy or resistance which can then change the direction of the development of a drug may be seen where tissue is *banked*, either virtually or physically, by large multi-institutional networks. This would enhance the quality and quantity of tissue analysis by applying a standardized approach to operating protocols, consent processes for future use and storage.[29]

Conclusions

The increasing demand for research biopsies in early oncology trials has not only an impact on infrastructure and logistics, but also on ethical aspects for patients and researchers. In this review, we have identified several aspects that highlight the current controversies surrounding research biopsies. Although acceptance rates for research biopsies are generally high and safe, we feel there is a need for improvement to reassure patients, but also to give patients a basis on which to make well-informed decisions. In this context, we propose that patient information sheets and consent forms should include detailed information concerning the biopsy procedure, including documentation of associated risks in relation to the tissue/organ to be biopsied. Patients should also be reassured that research biopsies bear no higher risk compared to standard diagnostic biopsies, as witnessed in several publications. Moreover, patients and advocates, including research ethics committees, should be educated about the progress made in the field of personalized medicine in oncology and the rationales for a *drug-tumor match* approach.

Clearly, where possible, we recommend that the number of such biopsies should be kept to a minimum and a search made for a surrogate marker if feasible. Recent advances in biomarker research have identified potential surrogate marker such as circulating tumor cells and circulating free plasma DNA. However, until these tests are available, we are reliant on research biopsies.

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