

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Inclusion of Biopsies in Clinical Trials of Oncology Drugs



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H&O What is the role of biopsies in clinical care vs clinical trials?

AT The biggest distinction is that in clinical care, a patient will derive direct benefit from the biopsy. For example, a biopsy will be used to make a diagnosis or change treatment. When used in clinical trials, biopsies can be defined by the scientific purpose they serve, and not all are associated with a direct benefit to the patient. Biopsies are considered integral when the results are used to determine the treatment the patient receives. In this case, the patient directly benefits. Integral biopsies were a component of recent trials of targeted therapy, such as the MOSCATO 01 study (Molecular Screening for Cancer Treatment Optimization) and the BATTLE study (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination). Another common reason for incorporating biopsies into clinical trial design is to assess the efficacy of treatment overall. This use of a biopsy is considered integrated. Results from these biopsies may be used to determine if the drug is working as anticipated, and whether researchers should enroll more patients or stop the trial. The patient who provided the biopsy sample, however, derives no direct benefit. Lastly, biopsies in clinical trials may be used to support correlative science, and to evaluate hypotheses in an exploratory manner. As with integrated biopsies, patients do not directly benefit from the results of an exploratory biopsy.

H&O Does inclusion of mandatory or optional biopsies impact enrollment in a clinical trial?

AT The literature suggests that when biopsies are optional

in a clinical trial, few patients choose to undergo them. However, mandatory biopsies may not necessarily be a barrier to enrollment for patients who have exhausted the standard-of-care treatment options. I work at MD Anderson, which is a quaternary cancer care center. Our patients tend to be highly motivated, and mandatory biopsies do not seem to affect their decision to enroll in

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clinical trials. In other treatment centers, there may be differences in terms of the patient population, patient education, and the availability of radiology and pathology specialists who can fulfill the requirements for tissue acquisition and processing that are associated with the clinical trial. These factors could influence enrollment rates.

H&O What are the potential adverse events associated with biopsies?

AT Biopsies are minimally invasive procedures, and needle placement is highly accurate when biopsies are performed with imaging guidance, such as ultrasound, computed tomography, or magnetic resonance imaging.

That being said, any time a needle is inserted into the body, there is a risk for adverse events, such as pain, infection, or bleeding. The type, frequency, and severity of adverse events can vary depending on the location of the biopsy. The risk of an adverse event is probably highest with lung biopsies because the insertion of a needle into the lung can cause the lung to collapse, which then might require treatment with insertion of a chest tube. In contrast, biopsies of subcutaneous nodules carry significantly lower risks of adverse events.

H&O What has research shown about the use of biopsies in clinical trials?

AT Our collaborative group of medical oncologists, pathologists, and interventional radiologists at MD Anderson have performed some research in this area. In one early study, we examined transparency, meaning how the risks and adverse events associated with biopsies in clinical trials are discussed in the informed consent. We reviewed an interventional radiology database to identify all therapeutic clinical trials in which image-guided research biopsies were performed from January 1, 2005, to October 1, 2010. Among 57 clinical trials, 67% contained at least 1 mandatory biopsy. Most of the studies failed to convey the risks and benefits of research biopsies in study protocol and informed consent.

We also evaluated how often the biopsy results of clinical trials are reported. We searched ClinicalTrials.gov for trials in oncology with completion dates between January 1, 2000, and January 1, 2015, with endpoint category terms including biopsy, biopsies, or tissue. Among 301 trials, only 50.8% reported any biopsy-related results. In a similar analysis of 866 research biopsies performed across 46 clinical trials, 61% of trials did not report results from research biopsies.

Other studies in the radiology literature have examined the complications associated with biopsies in clinical trials and the rate of yield of the tissue. In general, the rates of adverse events seen with biopsies performed in clinical trials were similar to those seen with biopsies performed in clinical practice as a component of the standard of care.

H&O What prompted the American Society of Clinical Oncology (ASCO) to issue an ethical framework regarding biopsies in clinical trials?

AT The recommendations from ASCO were drawn from a multidisciplinary meeting attended by oncologists, interventional radiologists, pathologists, patient advocates, and ethicists. Interest in this topic was based on several factors. Research biopsies are being incorporated into clinical trial

design at an increasing rate. Studies in the literature have identified a lack of reporting on biopsy results. There is uncertainty regarding whether biopsies in clinical trials have a significant scientific impact. Furthermore, from an ethical perspective, there is little guidance on when it may be appropriate to include mandatory biopsies in clinical trials, while taking into consideration patient safety.

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H&O What were some of the key recommendations?

AT The ethical framework addresses 3 main areas: how to maximize the scientific utility associated with biopsies, how to minimize the participant risk, and how to improve oversight of the process. To help patients and clinical trialists determine whether a research biopsy fulfills the goal of having an overall favorable risk-benefit ratio—and therefore meets ethical justification—the framework explicitly defines the scientific contribution to be expected from a biopsy, categorizes participant risk, and outlines when mandatory biopsy may be justified. Scientific contribution is defined as 1 of 3 categories: unknown utility, potential utility, and expected utility. The risk that a participant will experience a serious adverse event is categorized as low, moderate, or high. Mandatory biopsies are considered “ethically justified when there is a strong scientific rationale for their inclusion and when the study design maximizes likelihood of scientific benefit and minimizes risk to participants.”

Specific recommendations accompany each goal. For example, a recommendation was made to encourage journals to have authors submit the success rates and complication rates of biopsies performed for trials to “increase publication and dissemination of research biopsy safety and results.” Additionally, a recommendation was made that best practices should be promoted in the conduct of research biopsies to minimize participant risk. A charge was put forth to institutional review boards to adequately review the safety of research biopsies before approval of the trial design.

H&O Are there cases in which newer technologies, such as liquid biopsies, can fill the role of biopsies in clinical trials?

AT Liquid biopsy is an exciting field with quickly emerging data. ASCO and other clinical societies have begun to issue statements providing guidance on how to integrate liquid biopsies into care. In the future, it is likely that liquid biopsies will be able to replace tissue biopsy in certain cases. For now, however, tissue from a biopsy is still needed in many cases, particularly if the study is investigating the tumor microenvironment or whether the drug is acting as intended.

Disclosure

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Suggested Readings

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