ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Casting Doubt on the Scientific Utility of Post-treatment Biopsies in Phase 1 Trials

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H&O What is the goal of using post-treatment biopsies in phase 1 trials?

MR The putative goal is to learn something, such as whether a drug has hit the intended target, why a drug does or does not work, or the optimal dose or schedule for a drug.

The problem is that these biopsies waste time and money and carry a risk for injury. They can even cause death, as described in a study by Felip and colleagues that was published in *Clinical Cancer Research* in 2008. One patient, a 45-year-old woman with bilateral lung metastases whose disease had progressed after 3 lines of chemotherapy, died during a computed tomography–guided fine-needle biopsy; the specimen was being collected as a baseline for pharmacodynamic studies.

According to a study that was published by Gomez-Roca and colleagues in the *Annals of Oncology* in 2012, the "majority of patients" from 14 phase 1 clinical trials tolerated biopsy procedures well. In other words, some patients did not tolerate the procedures well. And, as the authors point out, there is a "lack of clinical benefit" from these procedures.

H&O Could you describe the design and results of your recent study on post-treatment biopsies?

MR For this study, which was first published online in the *Journal of Clinical Oncology* in late 2015, we identified 72 phase 1 oncology studies published between 2003 and 2010 in which patients had undergone at least one invasive, nondiagnostic post-treatment tumor biopsy for pharmacodynamic biomarkers. At least 1873 such biopsies were performed across the studies.

We found that just 5 of the 72 studies produced a statistically significant biomarker result that was cited in subsequent publications, and just 2 of these were cited by research groups other than those performing the original study. Furthermore, the use of post-treatment biopsies in studies became more common during the period we analyzed, increasing from 3 studies in 2003 to 19 studies in 2010.

Despite the increased use of post-treatment biopsies, their impact in phase 1 oncology studies and subsequent drug development remains uncertain, and no effect on subsequent dose or schedule was demonstrated in our data set. We have not analyzed more recent studies, but if the value is small or nonexistent, we need to seriously reconsider the continuing use of nondiagnostic biopsy studies in phase 1 trials.

H&O What made you decide to conduct this study?

MR I have always been concerned about the risks of invasive biopsies, and I did not believe such studies would be scientifically valuable because of sampling and assay issues. I also saw that researchers were doing these biopsies without a clear plan for analyzing the data. In the absence of a hypothesis, the studies are usually only exploratory, with a finite risk for a fatal complication. Given their prevalence, I consider such studies to be an epidemic of "pseudoscience."

H&O What are the lessons that you want people to learn from your study?

MR First, there is risk from drug development that goes beyond the risk from the drugs themselves—and that risk comes from the biopsies that may be required in a clinical trial.

Second, study participants should not assume that biopsies have significant scientific value just because the protocol has been through a variety of processes that include review by the US Food and Drug Administration (FDA). The FDA is very concerned about the drug doses administered to patients in phase 1 trials, and study protocols are regularly delayed owing to concerns about the rate of dose escalation. Never have I seen a protocol sent back with concerns about biopsy studies, however. What if the biopsies are riskier than the drug itself? The FDA is not thinking about the risk of post-treatment biopsies, and it should be.

Third, institutional review boards (IRBs) need to be aware of these risks, and stop "rubber stamping" such studies. Just because a protocol has been reviewed and approved by the FDA, the National Cancer Institute, or another learned committee, an IRB should not assume that all aspects of the protocol have been vetted for scientific value justifying the risk to the patient. If there is a risk to the patient and the scientific value is questionable, one has to question the ethics of the study. If IRBs were to start questioning these studies, that would have a huge impact.

Fourth, investigators need to understand the precise trade-off in terms of value vs risk of post-treatment biopsies. We will never learn that from haphazardly designed studies that measure biomarkers without a clear plan and try to make sense of the data after the fact.

H&O Have any other researchers looked at the value of post-treatment biopsies?

MR The older study that we built upon was published by Goulart and colleagues in *Clinical Cancer Research* in 2007. They found that the use of biomarkers in phase 1 trials had increased over the period from 1991 to 2002, and that biomarker utilization had made only "a limited and primarily supportive contribution to dose selection," the primary endpoint of phase 1 studies. They said that additional studies were needed to determine what type of biomarker information was most valuable to evaluate in phase 1 trials.

I coauthored a commentary about this study in 2007, and another group wrote a letter to the editor in 2008 that took issue with some of our conclusions. So there has been debate about this matter for several years.

More recently, in 2013, Saggese and colleagues wrote in *Oncology Reviews* about the increasing use of mandatory tumor biopsies in phase 1 studies and the challenges that these entail, including ethical concerns. They emphasized the need for accurate informed consent and discussed alternative strategies to guide the drug development process, such as noninvasive assays.

H&O Are there cases in which post-treatment biopsies should be used?

MR I think there will be cases in which it may be reasonable to proceed with using a biomarker endpoint instead of a long-term clinical endpoint. We do not want to create obstacles to testing drugs that have the potential to cure disease. However, this approach should be reserved for pivotal biomarker studies, and these studies must be designed in a way that produces robust results. The rate of false positives should be no higher than 5% and the rate of false negatives no higher than 10% to 20%, so that a phase 3 trial will have 80% to 90% power to detect the effect of the drug under study.

The bottom line is that we need to do fewer studies with post-treatment biopsies, and when we do decide to do them, we need to do a much better job.

Suggested Readings

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