ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Colorectal Cancer in Focus

The Promise of Liquid Biopsy in Colorectal Cancer

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H&O What are the limitations of tissue biopsy in cancer?

LD The main difficulty is the need to perform a surgical procedure or stick a large needle into the body in order to get a fresh tumor sample for biopsy. Surgical biopsies are uncomfortable and inconvenient to schedule, carry a risk of complications, and add to the cost of treatment. Another limitation is that the mutational status can vary dramatically among different tumors in the same person's body—especially in advanced disease—so sampling just one tumor may give an incomplete picture. Finally, a biopsy sample reflects a single moment rather than the overall course of the disease.

H&O What are the potential advantages of liquid biopsy?

LD The ability to perform a simple blood draw is a big advantage. Liquid biopsy allows a much easier way to get genetic information from a tumor without having to undergo the harmful and potentially dangerous biopsy, and the simplicity of a blood draw means that it can easily be repeated as needed. Another advantage is that liquid biopsy can reflect tumor heterogeneity, allowing all of the tumor mutations to be apparent.

H&O What are some potential applications for liquid biopsy?

LD There are some highly interesting potential applications for liquid biopsy. One application would be for early detection of cancer: the physician could simply draw a tube of blood and look for mutations that are markers for cancer. Another application would be to determine a tumor's genotype in order to select treatment. Measuring the amount of markers in the blood could also be used to detect residual disease after surgery and to measure response to treatment, disease recurrence, and disease progression. The physician could also look for mutations over time that are markers of treatment resistance in patients receiving targeted therapies.

H&O Could you see this technology being used for both clinical and investigational applications?

LD Absolutely—I see a future for all the applications we just talked about, both as a companion to investigative diagnostics and as a way to help patients directly in the clinic.

H&O What is the status of liquid biopsy?

LD Physicians already have access to approximately 6 or 7 assays that can be used to look at circulating tumor DNA, and all of them are quite good. There are also 4 or 5 companies that are trying to commercialize this technology; I also am part of a company that is trying to do that as well. I am encouraged by the fact that there will be multiple approaches to solve the same question, which will drive competition—and I think that is always good.

H&O What are the technological or scientific advances that have made liquid biopsies technically feasible?

LD Looking for mutations has never been easy. We have been able to use straight Sanger sequencing or pyro-

sequencing for some years in tissue where the tumor DNA is very abundant. But with the advent of digital genomics, we and others have developed the ability to look for rare mutations in the circulation of a cancer patient.

H&O What are some of the challenges in detecting circulating tumor DNA?

LD First, a blood sample may contain thousands of normal DNA molecules from cells throughout the body, compared with just 1 to 5 fragments of tumor DNA per milliliter of blood. It can be challenging to detect these rare mutant fragments of DNA, which is where digital genomics comes in—it allows us to see mutations that are rare.

H&O What are some of the most important research studies that have been done or are being done related to liquid biopsies?

LD Several ongoing studies are looking at this approach for a wide variety of clinical applications, including finding the genotype of a patient's tumor, tracking the disease over time, looking for residual disease, monitoring resistance, and early detection. The results from all of these studies are going to be very informative.

H&O What are some specific studies in colorectal cancer that you could discuss?

LD Most of these studies have been large, correlative, retrospective studies. One of the studies that is of particular interest is looking at the use of liquid biopsy as a screening tool to detect colorectal cancer at an early stage. Being able to detect colorectal cancer via a blood draw rather than undertaking colonoscopy would be tremendous.

H&O What do you expect the status of liquid biopsy for colorectal cancer to be in 5 to 10 years?

LD I am confident that in 5 to 10 years, we will have a blood test that can detect whether you have colorectal cancer at an early stage. We also will be able to determine the best first-line, second-line, and third-line treatments based on the analysis of circulating tumor DNA. Finally, we will be able to determine whether a patient is becoming resistant to therapy during the course of treatment.

Of course, the ultimate success of liquid biopsy will depend on the availability of targeted treatments. I think that the development of diagnostic techniques must go hand-in-hand with the development of treatments, and that clinical trials should incorporate both of these aspects. We are already seeing clinical trials that use circulating tumor DNA to select patients.

Financial Disclosures

Dr Diaz is the founder of Inostics, PapGene, and Personal Genome Diagnostics (PGDx), companies that focus on genomic analyses of cancers.

Suggested Readings

Dawson SJ, Tsui DW, Murtaza M, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *N Engl J Med.* 2013;368(13):1199-1209.

Diaz LA Jr, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. *J Clin Oncol.* 2014;32(6):579-586.

Diaz LA Jr, Williams RT, Wu J, et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. *Nature.* 2012;486(7404):537-540.

Diehl F, Schmidt K, Choti MA, et al. Circulating mutant DNA to assess tumor dynamics. *Nat Med.* 2008;14(9):985-990.

Forshew T, Murtaza M, Parkinson C, et al. Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. *Sci Transl Med.* 2012;4(136):136ra168.

Mouliere F, El Messaoudi S, Pang D, Dritschilo A, Thierry AR. Multi-marker analysis of circulating cell-free DNA toward personalized medicine for colorectal cancer. *Mol Oncol.* 2014;8(5):927-941.

Murtaza M, Dawson SJ, Tsui DW, et al. Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. *Nature.* 2013;497(7447):108-112.

Thierry AR, Mouliere F, El Messaoudi S, et al. Clinical validation of the detection of KRAS and BRAF mutations from circulating tumor DNA. *Nat Med.* 2014;20(4):430-435.