



CAP Lung Cancer Medical Writers' Circle

Epigenetic Therapy for Lung Cancer

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Changes to a cell's DNA such as mutations and deletions have long been known to be part of what causes cancer. DNA is made of long chains of nucleic acids which form genes that code for RNAs. These RNAs in turn make proteins. Proteins conduct the many complex tasks that cells must continually perform and keep balanced in order to function like a normal cell. When portions of the DNA are mutated or deleted, the function of proteins made may be changed, or may be lost all together. These changes to DNA sequences form the *genetic* basis of cancer.

But what makes a cell a cell is more than just a lot of DNA making proteins. The human genome is big, about 3 billion pairs of nucleotides. Not all of it needs to be working all of the time, and the cells in your body need different things from the DNA at different times. If you think of the DNA in a cell as an incredibly complicated machine, you see that a machine that complex needs an operator to control it. Epi-genetics (Epi- Greek for upon, or over) is the study of the things that make a cell what it is by anything other than the sequence of its nucleic acids. So how could something change what a cell is if it isn't DNA? Let us say there is a protein that keeps a normal cell from dividing into two cells. A cancer cell missing that protein may allow itself to divide and make more cancer cells uncontrollably *even though the DNA that makes that protein is completely normal*. How could this happen? How could a normal gene fail to do its job? One way is that the gene is *silenced*. Silencing occurs in a few ways, one of which is the methylation of a gene's promoter. Think of the promoter as an on/off switch for a gene, and one way to turn it off is to methylate it. Once the gene is methylated, the protein is not made and the cell is allowed to divide uncontrollably.

What would be the purpose of turning off potentially helpful proteins? First, during development, which is the time when an organism is forming organs and growing larger, the cells behave very differently than when they become normal, mature cells. Second, a brain cell and kidney cell are completely different, *yet they have completely identical DNA*. It is the operator, *the epigenetic machinery*, of a cell that allows different proteins to be produced at different times and in different parts of the body that allow cells to develop in to normal structures and perform specialized tasks. And, unfortunately, just like genetics where normal DNA can be changed to cause cancer, things can go wrong with the epigenetic machinery that leads to cancer.

Investigators at Johns Hopkins Hospital in Baltimore performed a clinical trial for patients with advanced unresectable or metastatic lung cancer using a new kind of treatment: Epigenetic Therapy.(1) The idea behind the trial was that if a cancer has figured out how to use epigenetic machinery to turn off proteins that keep it from growing, maybe we can use epigenetic therapy to turn those useful proteins back on. A combination of two drugs which target epigenetic machinery, entinostat and azacytidine, which had previously only been used with success in cancers of blood cells (leukemia and myelodysplastic syndrome). The 45 patients on trial had received a median of 3 prior therapies. The trial regimen was very well tolerated with the most frequent side effects being lowering of white blood cell counts, fatigue, and irritation at the site of injection of one the drugs. One patient on this trial had a complete response to therapy (Figure 1), and another patient had a major partial response. Ten patients had stable disease, one for nearly a year and a half. Another exciting development from the trial is that a simple blood test may help us identify the patients who will benefit from this therapy. (Figure 2)

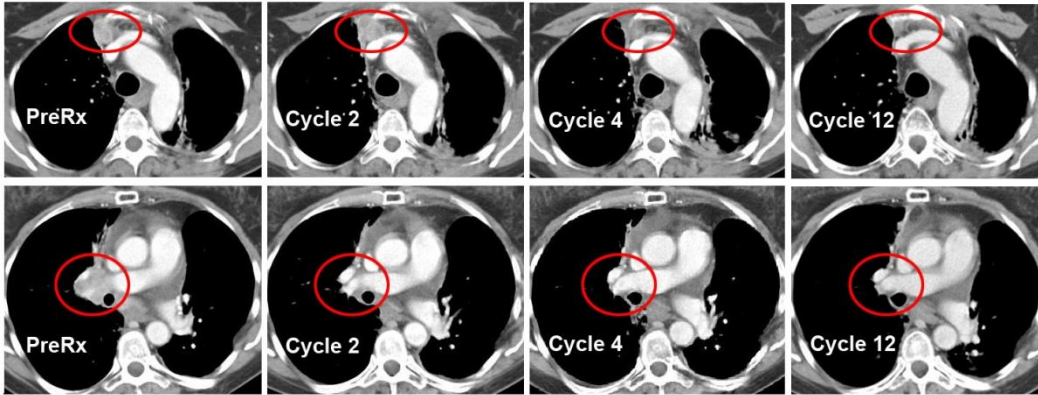


Figure 1. CT scans of the chest of a patient who had a complete response to epigenetic therapy. CT scans shown are over a 12 month period demonstrating persistent tumor shrinkage after many months of therapy.

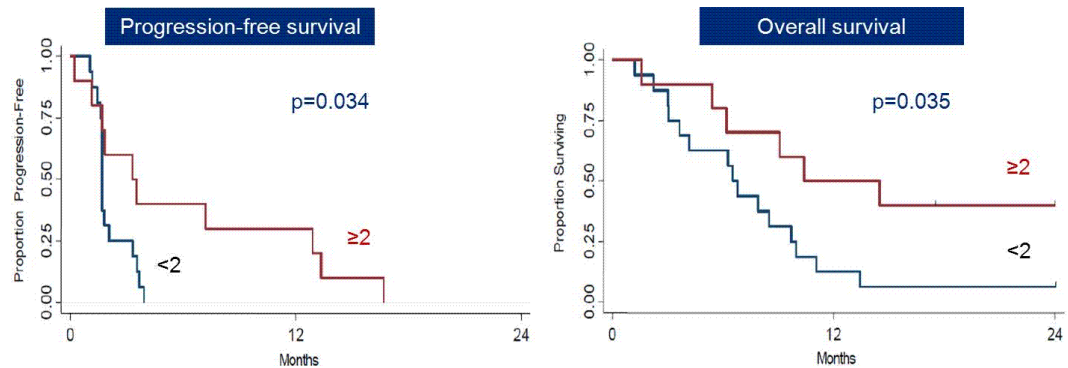


Figure 2. Kaplan Meier Curves showing that results of a blood test may identify patients whose disease will progress later and live longer in response to epigenetic therapy.

In addition to patients who benefit from epigenetic therapy itself, there may be patients who benefit from epigenetic therapy before chemotherapy. When study patients were followed, many were noted to be having better than expected responses to chemotherapy and living longer, *even though their disease grew while receiving epigenetic therapy.* (Figure 3)

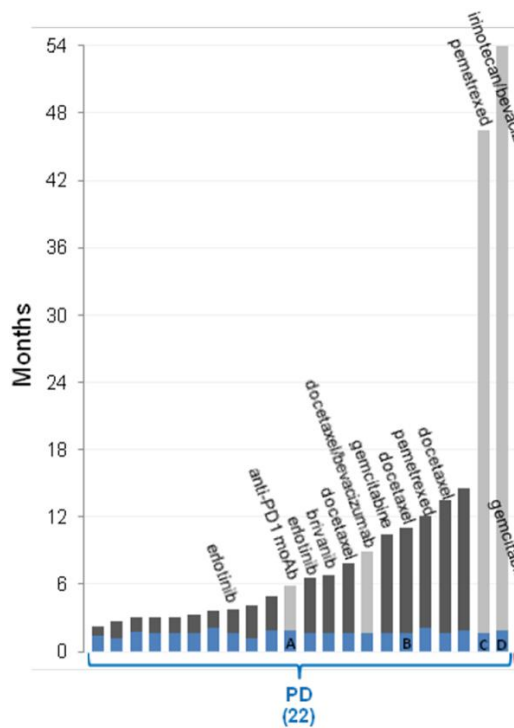


Figure 3. Patients who had progressive disease on epigenetic therapy. The height of the blue bar indicates the amount of epigenetic therapy received. The height of the gray bar indicates how long the patient survived after being enrolled to the clinical trial. Light gray bars indicate that the patient is still alive.

Just as certain proteins help keep cells in check, they may also help chemotherapies work better or help cells die when they are supposed to. Epigenetic therapy may be allowing cancer cells to respond better to chemotherapy. Hopkins investigators are currently developing a trial to look specifically at the idea of whether epigenetic therapy improves how well chemotherapy benefits the patient.

Epigenetic Therapy represents a new and promising kind of treatment of lung cancer, though it remains experimental and available only in a clinical trial. As the trial showed that some lung cancers can be treated to great success with epigenetic therapy, and that this same therapy may improve the use of other therapies, we can expect to see great interest in investigations exploring these kinds of treatments in the near future. Patients with lung cancer interested in trials of epigenetic therapy should talk to their oncologist or see what trials may be available at Johns Hopkins.

References

1. Rosalyn A. Juergens, John Wrangle, Frank P. Vendetti, et al. Combination Epigenetic Therapy Has Efficacy in Patients with Refractory Advanced Non–Small Cell Lung Cancer *Cancer Discovery* 2011: 598-607.

Glossary

Genetics - The study of the molecular structure and function of genes

Genes – The genetic basis of heredity. Genes are made of nucleotide segments of DNA, which when transcribed form RNA. RNA when translated forms proteins.

Epigenetics – Study of heritable changes which occur without changes to the nucleotide sequence.

Silencing – Absence of gene expression by non-genetic means.

CT – Computed Tomography. A common technique in radiology for imaging tumors.

Kaplan-Meier Curves – A graphic estimation of the time a population reaches any given endpoint, such as when patients disease progresses or time to death.