War on Cancer

by Ralph Moss, PhD
www.cancerdecisions.com

Falling Down the Rabbit Hole!

Scientists studying triple-negative breast cancer at Vanderbilt University recently made a disturbing discovery. Even after receiving chemotherapy before surgery, most patients still had multiple genetic mutations in their tumor cells. Justin Balko, PhD, and Carlos Arteaga, MD, presented these findings at the San Antonio Breast Cancer Symposium, December 4–8.

Triple-negative breast cancer patients are routinely treated with chemotherapy to shrink their tumors prior to surgery. This is called neoadjuvant chemotherapy (NAC). But most still had multiple genetic mutations in their tumor cells, according to a study by Vanderbilt-Ingram Cancer Center (VICC) investigators.

"The standard of care for many patients with triple-negative breast cancer is to administer chemotherapy before surgery to shrink the tumor," said Balko. "Unfortunately, about 70% of patients still have some residual disease at the time of surgery, despite treatment."

Balko looked at residual tumor tissue from 114 patients with triple-negative breast cancer after they received NAC. They evaluated DNA from 81 tumors and examined 182 oncogenes and tumor suppressors that are often altered in human cancers.

Instead of finding similar genes affecting the patients, however, they found a diverse set of altered genes.

"We already knew that triple-negative breast cancer is driven by a diverse group of genetic alterations," Balko said. "So, in one way, we fell further down this rabbit hole...."

But putting a positive spin on this diversity, she said that they found some promising therapeutic targets.

Tip of the Iceberg

These genetic mutations are just the tip of an iceberg. An article in *Science* last year contained an article with the astonishing assertion that in many cases of cancer there were thousands of separate mutations in each tumor.

> We now know that there are usually between 1,000 and 10,000 somatic substitutions [mutations] in the genomes of most adult cancers, including breast, ovary, colorectal, pancreas, and glioma [brain]. ... There are cancer types that generally carry relatively few mutations–for example, medulloblastomas, testicular germ cell tumors, acute leukemias, and carcinoids ... whereas others, such as lung cancers and melanomas, have many more mutations (occasionally more than 100,000). ... Even within a particular cancer type, individual tumors often display wide variation in the prevalence of base substitutions. (Stratton 2011)

Imagine, then, trying to devise a treatment regimen that targets thousands of separate mutations! This is what Balko meant when she referred to falling down the rabbit hole. Scientists who believe the somatic mutation theory of cancer are facing a dismaying prospect. Some rare types of cancer may yield to genetically based treatments. But the typical kinds of cancer have too many mutations to cover with even a panoply of drugs. By contrast, if scientists focus on the abnormal metabolism of cancers, they will find a few conspicuous targets that are common to most cancers. They can then devise drugs and other methods of modifying how cancer cells derive their energy – such as the excess uptake of glucose.

Chemo Assay Yields Better Results

DiaTech is a company that also has a Vanderbilt connection. The company that provides the MiCK assay, a chemosensitivity test for the live tissues of cancer patients. This test helps determine, on an individual basis, which drugs are likely to work and which will not work. Although in the past the "cancer establishment" has scorned this type of test, there is growing evidence that they yield better than average results.

At the San Antonio cancer symposium, DiaTech scientists offered evidence of this. When doctors used the