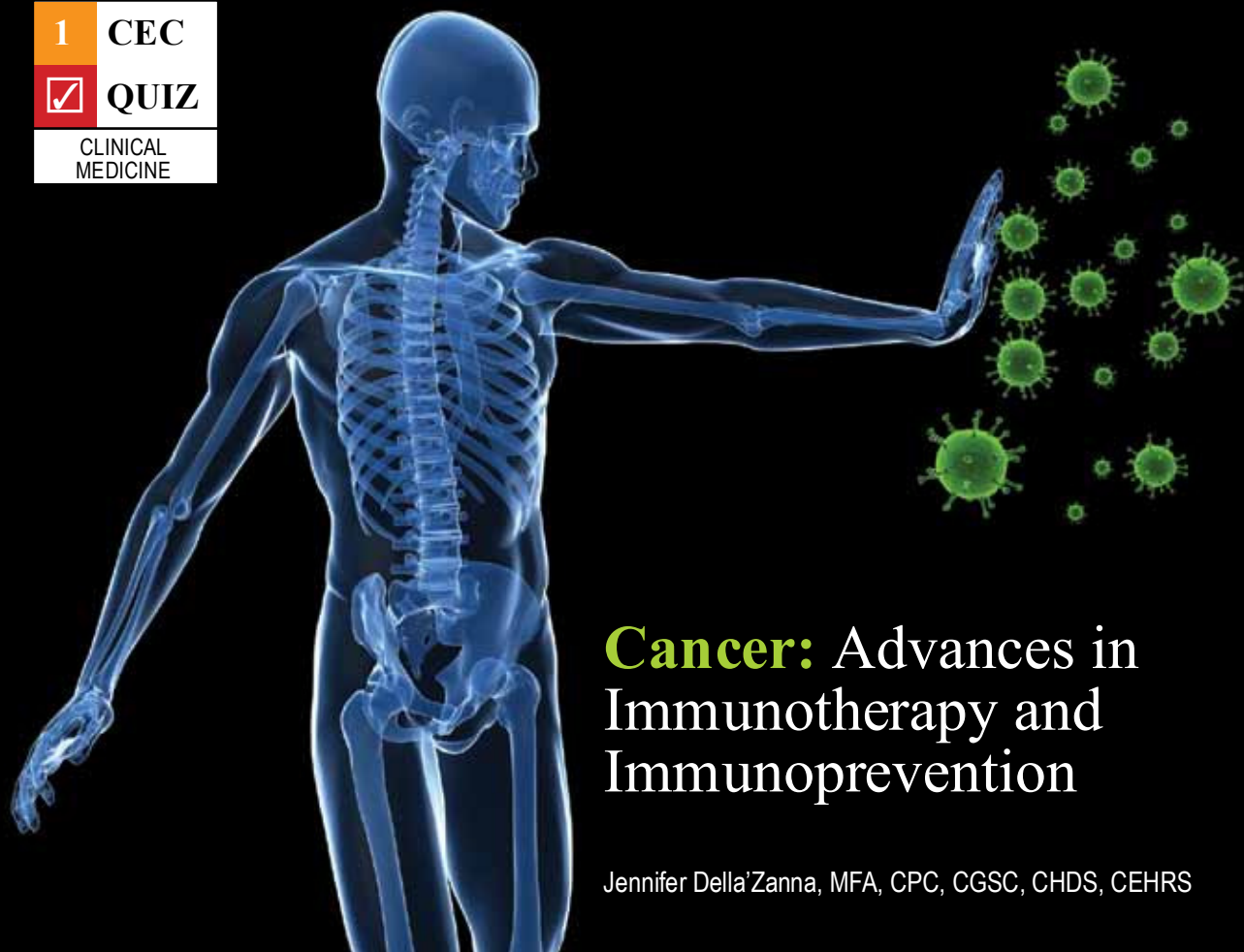
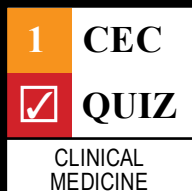




Cancer: Advances in Immunotherapy and Immunoprevention

Jennifer Della'Zanna, MFA, CPC, CGSC, CHDS, CEHRS

In June 2018, the mainstream media picked up a single case study based on a report in the medical journal, *Nature Medicine*, about a 49-year-old woman with stage IV breast cancer treated at the National Cancer Institute (part of the National Institutes of Health (NIH) in Bethesda, MD). She was treated in a clinical trial that used experimental procedures to enhance her own immune cells to treat her breast cancer that had already spread to several organs. It was newsworthy because she has been disease-free for two years. At the start of this unapproved treatment, she had been given three months to live. The NBC article is here:

<https://www.nbcnews.com/health/health-news/highly-personalized-treatment-saves-breast-cancer-patient-n879841>.

Results like this always get a lot of attention for the “new” treatment that provides such incredible results. People tend to believe we’re on the verge of a major, miraculous breakthrough and, surely, there will be no more cancer as soon as everybody can get the new and improved treatment. While we may be on the edge of a major breakthrough, “edge” means different things to cancer researchers than it does to the general public. This treatment is, by no means, new. That does not mean it isn’t worth celebrating, and it certainly does mean that this is a treatment we should all know about as members of the health care community. Of course, we may be seeing more of this type of therapy in our work, but we will probably be asked by many of our friends for our opinions about the results of this study, as well.

Immunotherapy

The concept of immunotherapy has been part of cancer treatment for over a century, although it wasn’t until we decoded the human genome that we saw the first targeted drugs we now called “biologics.” What has happened since in the laboratory has been a result of that particular incredible breakthrough. In this type of cancer treatment, the immune system is activated to work against a cancer already present in the body. This is a cancer *treatment*, not *prevention*. In the case reported by *Nature Medicine*, the woman had recurrent, metastatic breast cancer that had failed to respond to traditional chemotherapy.

There are two types of immunotherapy: passive and active. In *passive immunotherapy*, the body's own immune system is not activated, but agents (drugs) that act in a similar way to our immune systems are introduced that kill tumor cells. There are fewer side effects and less toxicity with this type of therapy (treatment). Unlike chemotherapy, which kills all cells, good and bad, these new agents target cancer cells specifically. One example of this type of agent is trastuzumab, which is a monoclonal antibody used to treat HER2/neu-positive breast cancer. *Adoptive immunotherapy*, a type of passive immunotherapy, is currently being studied for use in several types of cancer, including some of the worst—malignant melanoma.

In active immunotherapy, the goal is to have the body's own immune system generate antibodies that target cancer cells. This immune stimulation can cause either a specific or nonspecific response. A treatment with a targeted response is *specific*. An example of this would be deriving a treatment directly from the patient's own cancer cells. Although it is highly specific, the treatment is also very limited. All the conditions from which it was created must be identical in order for it to work again.

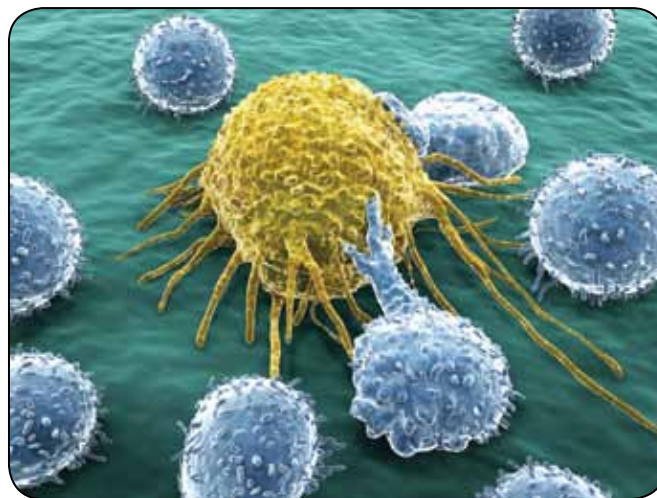
If the drug causes a generalized activation of the immune system, it is considered *nonspecific* stimulation. Although this treatment is less targeted, it is more likely to work in a number of cells because of its more generalized response.

The case reported by *Nature Medicine* was part of a study using autologous *tumor-infiltrating lymphocytes* (TILs). This experimental therapy removes some of the patient's white blood cells that have migrated into tumors. The researchers then attempt to identify the specific T-cells they expect to be able to fight the cancer and grow them in large quantities in the lab. These cells, measured in the millions, are then reintroduced into the patient's circulation.

TILs have been found to be a good predictor of treatment outcomes. This new study result takes it a step further. The ability of TILs to trigger immune reactivity may be an inroad to what the NIH has been chasing for decades—an antitumor vaccine.

Immunoprevention

Solid tumors generally cannot be detected until they measure 1 cm in diameter. Depending on how quickly the tumor grows, that may mean a cancer can go undetected for years. We have had success in immunoprevention of cancers that are initiated by an infectious process, simply by vaccinating for the infection. An



example of this would be the HPV vaccine, which protects against many strains of the human papillomavirus infection, which is a leading cause of cervical, vaginal, and vulvar cancers in women and penile and rectal cancer in men.

There is evidence that solid tumors express certain proteins before they become invasive (i.e., malignant), prompting a mild immune response. This response has been studied in both breast and colon cancers. Although the immune system seems to be able to recognize preinvasive tumors, we still have better results with therapy in these cases than prevention attempts. What we know is that the immune system is able to tell the difference between “self” and “non-self,” and it is able to tell the difference between “self” and “altered self,” but many tumors have the ability to evolve in such a way as to evade the immune system's identification process.

Asad Umar, DVM, PhD, Chief of the Gastrointestinal and Other Cancers Research Group in the National Cancer Institute, notes that more than 80% of the tumor burden for humans is not related to infection, and it is for those tumors we are now most focused on finding an immune response. He says, “Cancer immunoprevention is conceptually different from immunotherapy, which aims at stimulating immunity in patients only after the tumor onset; however, the same immunological means can be used . . . in immunoprevention.” (Umar, Feature Article: Cancer Immunoprevention 2013)

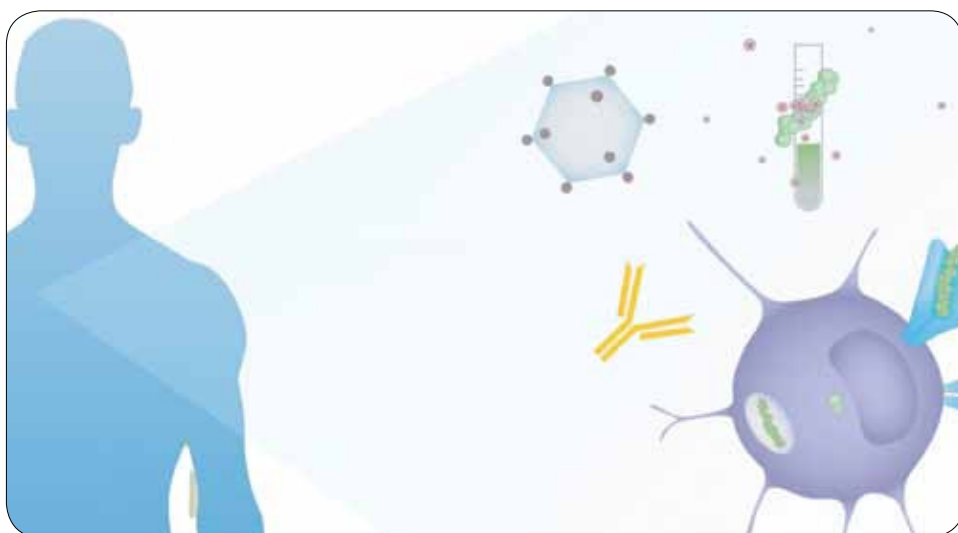
Currently, the only primary prevention of non-virus-associated tumors that exist are aspirin for colon cancer and tamoxifen for breast cancer (which is used as therapy and then used to prevent recurrence). Several studies of vaccinations for prevention of recurrence of high-risk melanoma show promise. And, as we see with the study reported in *Nature Medicine*, prevention of secondary breast cancer is an expanding field. Several trials are actually being conducted with HER2/neu positive cancers, as well as with other targeted antigens.

Although there are some very promising trials, there

have been cancer vaccine trials that have demonstrated no benefit, or even a detrimental result. There are barriers to developing vaccines for cancer. First, for many tumors, it is difficult to find a population of high-risk participants.

The patients must be free of disease but have a known risk of developing that cancer. A clear determination of probability of developing certain cancers is simply not there yet. A second barrier to development of vaccines to target specific cancers is that they are still very difficult and expensive to produce. Without that clear definition of who would benefit from the vaccines, even the ability to produce the vaccines doesn't mean they will be widely adopted. Another major issue that has slowed progress is that all cancers suppress the immune system, and an active immune system is needed for vaccines to work.

Should the results of the woman in the study give us



hope? Of course. Is there still a lot of work to do? Of course. Not much has changed for the foreseeable future, as far as treatment of new and recurrent cancers, and certainly not for prevention. But cancer treatment and prevention studies continue with billions invested in the research every year and scientists making discoveries every day. We should continue to celebrate the victories and infuse with hope all encounters with patients who struggle with cancer diagnoses. There are talented researchers working hard to find the cures we all want to hear about. **P**

Jennifer has worked in the allied health care industry for more than 20 years in every capacity from receptionist to practice manager. Currently, she writes and edits courses, study guides, and online and print articles about clinical subjects, medical coding, transcription, electronic health records and the use of technology in health care.

References

- Harris, Timothy J, and Charles G Drake. 2013. "Primer on Tumor Immunology and Cancer Immunotherapy." *Journal for ImmunoTherapy of Cancer* 12–21.
- Harrison, Carlos. 2018. "Using Autologous Tumor-Infiltrating Lymphocytes to Mediate Tumor Regression: Promising Outcomes in Experimental Research." *Cancer Therapy Advisor*. July 30. Accessed July 31, 2018.
- Marquez, Juan P, Sasha E Stanton, and Mary L Disis. 2015. "The Antigenic Repertoire of Premalignant and High-Risk Lesions." *Cancer Prevention Research* 266–269.
- Smit, Marie-Anne D, Elizabeth M Jaffee, and Eric R Lutz. 2014. "Cancer Immunoprevention—The Next Frontier." *Cancer Prevention Research* 1072–1078.
- Umar, Asad. 2014. "Cancer Immunoprevention: A New Approach to Intercept Cancer Early." *Cancer Prevention Research* 1067–1070. 2013. "Feature Article: Cancer Immunoprevention." *CPN Highlights*, Fall: 3-5.
- Wojtowicz, Malgorzata E, Barbara K Dunn, and Asad Umar. 2016. "Immunologic approaches to cancer prevention—current status, challenges, and future perspectives." *Seminars in Oncology* 161-172.