Use of the Anti-Parasitic Drug Ivermectin to Treat Breast Cancer

BY PETER P. LEE, MD

Despite significant advances in the treatment of breast cancer, triple-negative breast cancer (TNBC) remains the most difficult subtype to treat. As the name implies, triple-negative breast cancer cells lack three key proteins—receptors for the estrogen and progesterone hormones, and the protein HER2—which are targets for many effective breast cancer drugs today.

With that in mind, our team wanted to uncover new therapeutic combinations that could treat TNBC and provide more treatment options to these patients.

Immune checkpoint inhibitor (ICI) therapy has emerged as a revolutionary approach that harnesses a patient’s own immune system to treat cancer. However, checkpoint inhibitors as single agents are only effective in a subset of patients and cancer types. They’ve had little impact in breast cancer.

Recent studies suggest that efficacy of checkpoint inhibitors is primarily limited to cancers already infiltrated by T cells—often termed “hot” tumors. In contrast, “cold” tumors have little to no T-cell infiltration and generally do not respond to ICI therapy. As such, there is considerable need to identify drugs capable of priming breast tumors (turning “cold” tumors “hot”) to synergize with checkpoint blockade.

A recently described phenomenon, termed immunogenic cell death (ICD), is a form of cell death that stimulates the host immune system. We reasoned that an agent that induces ICD of cancer cells without suppressing immune function would be ideal for combination with ICI therapy.

Seeking such an agent among FDA-approved drugs, our group found that ivermectin, an anti-parasitic drug used worldwide since 1975 to treat close to 1 billion people primarily for river blindness and other parasitic infections, promotes ICD in breast cancer cells. Among our other findings was evidence that ivermectin modulates the P2X4/P2X7 purinergic pathway, suggesting that ivermectin may further harness tumors’ intrinsic high extracellular levels of ATP for anti-cancer activity.

These promising in vitro results prompted us to move forward into vivo studies using a common animal model of TNBC. In this model, breast tumors are “cold,” indicating little or no infiltrating T cells. Ivermectin treatment led to robust T-cell infiltration turning cold tumors into hot tumors with cancer cells showing markers of ICD in vivo.

The ability to turn TNBC tumors from cold to hot suggested that ivermectin could synergize with ICI therapy (such as with anti-PD-1 monoclonal antibodies). Immune checkpoint inhibitors block the PD-1 protein, which acts as a brake on T cells, thus helping the immune system do what it is designed to do: eradicate cancer.

Our findings on this novel therapeutic combination published recently in npj Breast Cancer Journal (2021; https://doi.org/10.1038/s41523-021-00229-5). This is the first time a research team has demonstrated that checkpoint inhibitors can be used to successfully treat breast cancer—when combined with ivermectin, an inexpensive, existing safe drug.

Based on its novel dual mechanisms of action (anti-cancer and immunomodulatory) in cancer, ivermectin may also potentiate the anti-tumor activity of other FDA-approved ICIs. Ivermectin is safe and inexpensive at roughly $30 a dose, making it attainable for everyone including cancer patients in developing countries.

These preclinical findings suggest that the combination of ivermectin and anti-PD1 antibody merits clinical testing in breast cancer patients. We are now planning to test optimal dosing levels for a potential first-in-human clinical trial. Interestingly, in the last year, ivermectin has also demonstrated efficacy against COVID-19, and it is being tested in dozens of clinical trials to both prevent and treat the virus.