Michael Cecchini, MD

New Research on Colorectal Cancer

Innovative therapies are expanding treatment options for patients with cancer and changing the way many cancers are managed. Unfortunately, some types of cancer have benefitted less than others. The standard treatment for colorectal cancer (CRC), for example, remains cytotoxic chemotherapy, even though CRC is the third most common cancer and the third most common cause of cancer death among both men and women.

Michael Cecchini, MD, Assistant Professor of Medicine (Medical Oncology), Co-Director of the Colorectal Program in the Center for Gastrointestinal Cancers at Smilow Cancer Hospital and Yale Cancer Center, and a member of Yale Cancer Center's Developmental Therapeutics Research Program, has been working to change that. His research got a boost and a large vote of confidence last fall when the National Cancer Institute awarded him a K08 grant, more formally called a Mentored Clinical Scientist Research Career Development Award.

"What it really does is 'protect' my time," said Dr. Cecchini, "so I can devote more time to research that advances the field of colorectal cancer."

The research grant aims to investigate multiple clinical trials for patients with colorectal cancer, initiated by Dr. Cecchini under the mentorship of Patricia LoRusso, DO, Professor of Medicine (Medical Oncology) and Associate Cancer Center Director for Experimental Therapeutics. The first trial is a Phase II study in which patients will be treated with a combination not normally used against colorectal cancer: temozolomide (TMZ), a well-known drug, and olaparib, from the relatively new class of drugs of PARP inhibitors.

TMZ has been used for some time against gliomas and glioblastomas (GBMs). The drug damages a tumor cell's DNA, which can slow or stop the tumor's growth. It is well established in the literature that gliomas and GBMs became more sensitive to TMZ when a protein called O6-methylguanine-DNA methyltransferase (MGMT) was hypermethylated in the tumor—that is, absent or silenced. MGMT is crucial to the repair of damaged DNA caused by TMZ, so when MGMT is absent, the tumor's DNA cannot repair itself.

"Reviewing the literature, I realized that the same defect—the loss of MGMT—is present in colorectal cancer in up to 40 percent of cases," said Dr. Cecchini. "That has been historically underappreciated. MGMT is a potential biomarker we can identify in these colorectal tumors. So, I thought, 'Ah ha! Maybe we can think about this subtype of colorectal cancer the way we think about GBM and use similar drugs on colorectal cancer, which we normally would never think to use.' I'm also trying to take it a step further by adding on drugs to synergize with TMZ for more efficient killing of colorectal cancer."

The synergy comes from adding the PARP inhibitor, olaparib. PARP inhibitors kill cancer cells by hindering DNA repair. "So, you impair DNA repair with one approach," said Dr. Cecchini, "and then add to that a PARP inhibitor." The trial is identifying patients that have MGMT promoter hypermethylated colorectal cancer and offering enrollment in the trial of temozolomide plus olaparib.

"This is also an opportunity to develop biomarker-driven therapies so that we can give the right patients the right treatment at the right time. That's really what I'm interested in developing," said Dr. Cecchini, "because after chemotherapy we have few options to offer to our patients with colorectal cancer." The trial is enrolling patients now.

Dr. Cecchini's other clinical trial, which he hopes to open by the end of 2022, will combine TMZ with an inhibitor of ATR, another protein involved in DNA repair. "This is a true Phase I study," said Dr. Cecchini. "It will be the first clinical experience anyone has had with this combination of drugs, and it's potentially a more potent combination than TMZ and olaparib." The trial's goals are to determine toxicity and safe dosage in anticipation of a Phase II trial.

The most urgent need for patients with colorectal cancer, says Dr. Cecchini, is immunotherapy. He is intensely curious to see whether the drug combinations he is studying will stimulate the immune system to the point where it begins attacking and killing cancer cells on its own.

"We think that certain therapies increase the tumor's mutational load," said Dr. Cecchini. "The more mutations the tumor has, the more likely that one of the mutations will lead to a neoantigen that can be highly recognized by the immune system."

In some lab experiments, TMZ has been shown to have that effect. If TMZ can do that on its own, Dr. Cecchini reasoned, maybe adding other agents that damage DNA will further increase the mutational burden and let the immune system lock on to the cancer better. "If we can do that," he said, "more T-cells will enter the tumor microenvironment to fight the colorectal cancer."

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—Dr. Michael Cecchini

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