

The Final Frontier? Inhibitor Cocktails to Stamp out Cancer

The use of mutation-specific, inhibitor drugs to fight cancer has been growing in popularity around the world. In fact, over the last ten years, the prescription rate of inhibitors over cytotoxic chemotherapy has more than tripled according to the National Institute of Cancer. Cytotoxic chemotherapies are simply not targeted enough to most cancer cells and still too detrimental to the body as a whole. Indeed, in 2004, the *Journal of Oncology* published a revealing table with cytotoxic chemotherapy as the sole treatment: the 5-year survival rate was on average, less than 2.2% for hundreds of thousands of patients across twenty-two cancer types: the most being 41%, the least, zero. The statistics, though challenged from every corner, were not surprising considering that cytotoxic chemotherapy is a direct derivative of mustard gas, a WW1 and WW 2 chemical warfare agent.

However, while inhibitors are increasingly and remarkably effective in reducing tumors and cancer cell counts in a short amount of time, and with a fraction of the toxicity compared to their chemotherapy counterparts, cancer resistance to inhibitors remains an ongoing problem.

Inhibitor drugs are molecules that bind uniquely to a cancer cell's surface and block an aspect of that cell's functionality. For example, PARP inhibitors, designed to stop breast cancer, bind to an enzyme pathway found distinctly on breast cancer cells with a BRAC genetic mutation. The PARP molecule's attachment prevents the cell from performing DNA repair, leading to its death.

What has baffled doctors however, is that after remission from inhibitor therapy, a resurgence of cancer almost always occurs and often at a more aggressive rate. Over the last several years, doctors have tackled the problem by treating patients with a secondary inhibitor, only to find secondary resistance and with a patient, more debilitated by the continuous use of drugs and emergence of aggressive cells.

"It's becoming clear to the medical establishment that a cocktail of inhibitor drugs need to be given simultaneously," Jeffrey Epstein remarked, founder of the Program for Evolutionary Dynamics at Harvard University. The department or PED, studies the evolution of microbiology with the use of mathematics, including viruses and diseases such as cancer.

A New York financier and science philanthropist, Jeffrey Epstein funded the PED's huge strides in detailing cancer resistance to inhibitor drugs. Under the direction of Martin Nowak, a Biology and Mathematics Professor at Harvard, the PED designed mathematical models showing exactly how a minority of mutated cancer cells are either immune from the start of treatment, or evolve through reproduction, to become immune to an inhibitor drug. Their models also showed how even a single mutated cell can quickly evolve to tumor level. For example, approximately half of non-small cell lung cancer cases with mutations to EGFR TK inhibitors became resistant from a single mutation of the protein T790M within the EGFR kinase domain.

PED's work caught the attention of Dr. Bert Vogelstein, the Director of the Ludwig Center for Cancer Genetics and Therapeutics at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine. Dr. Vogelstein was studying resistance to a colon cancer inhibitor called panitumumab. Enlisting Dr. Nowak's help,

Vogelstein and the PED designed a mathematical model from the tumorous tissue of 28 colon cancer patients at Johns Hopkins about to embark on a course of panitumumab treatment.

Nowak's findings were extraordinary: they showed that even before treatment began, less than .0001% of cells carried resistance to the inhibitor but could quickly evolve over the course of a year to predominance and tumor level. Based on these findings, amongst others, Dr. Vogelstein and Dr. Nowak concluded that a cocktail of inhibitor drugs and in the right proportion, must be used to target all colon cancer mutations.

Cocktails of inhibitors are starting to creep into clinical trials and results, though too early to assess, have been promising. Just a few years ago, the FDA approved the first combined inhibitor drugs as a single pill. Prior to that the FDA required that the merit of each active ingredient be proven before it could be added to another. Just a few months ago, the FDA approved the first combined inhibitor therapy pill for melanoma: Dabrafenib and trametinib, designed to block certain BRAF enzyme pathway genetic mutations. These mutations occur in approximately 50% of melanoma patients and can be identified with a diagnostic test. Finally, it seems that the resistant sequence of cancer is unavoidably clear. Scientists have a new understanding of the typical resistant pathways that come to dominance for each cancer and these have to be circumvented.

So far after one year of clinical trial treatment on the combined pill, Dabrafenib and Trametinib, 41% of melanoma patients were progress-free compared with only 9% in the monotherapy Dabrafenib arm. The inhibitor combination also reduced the resistant emergence of secondary cutaneous squamous cell carcinoma, down to 2% from 19% in the Dabrafenib monotherapy group.

The FDA's accelerated approval of combined inhibitor drugs for cancer will turn the industry on its head: pharmaceuticals such as Roche and GlaxoSmithKline can now actively put money towards developing such pills and funding trials to support them. Currently for example, GlaxoSmithKline is sponsoring clinical trials that compare inhibitor combinations for colon cancer: dabrafenib/panitumumab and dabrafenib/trametinib/panitumumab combinations compared to a 5-fluorouracil-based chemotherapy.

The challenge however is still daunting: each cancer requires its own tailor-made inhibitor, and within each tumor, various inhibitors are needed to target the variety of mutations. For example, gastric adenocarcinomas, stemming from amplification of the growth factor receptor gene c-MET, only respond to novel inhibitors of the MET tyrosine kinase, leading to the initiation of a genotype-directed clinical trial. The FDA has approved a handful of inhibitors, but many more are needed. To date, the 5 year survival rate for fully metastasized pancreatic is still only 2%, metastasized lung: 4%, melanoma: 16%, colon: 12%, and distant metastasized breast: 24%.

Secondly, there are few clinical trials that offer inhibitor combinations: the concept is still novel and most pairings with other drugs tend to be with cytotoxic chemotherapies— since funding to a large degree comes from the pharmaceutical companies, seeking to prolong their older inventories' shelf-life. Less cynically, countless trials conclude that cytotoxics in conjunctive therapy with inhibitors can, with certain cancers, increase survival by a month or two.

“A third major challenge to developing inhibitor cocktails is the need for better mutation analysis,” Jeffrey Epstein points out, whose foundation, the Jeffrey Epstein VI Foundation, funds cutting edge cancer research around the world. PED’s studies have shown that most solid tumors contain 40 to 100 mutations and that only 5 to 15 of these at any given time actually drive tumor growth. Isolating these mutated drivers via biopsy however can be onerous on the patient, particularly if the biopsy is extracted from an organ, lung or bone and if it has to be repeated over time. Looming on the horizon is the promising CTC circulatory tumor cell microfluidic chip test, a blood test developed at Massachusetts General that can isolate and identify cancer mutations at any given time. To date, the test has identified more than 1,200 cancer-causing genetic mutations, the largest collection in the world, but the test is not yet FDA approved, nor is it available in any clinical trials.

Lastly, combination proportions will need to be determined as cocktail inhibitor trials become the norm, and that of course, like everything else, will take time.