Cancer Cells Mutate to Resist Chemotherapy

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It is a well-known that bacteria mutate when exposed to antibiotics in order to survive. This has led to an increasing incidence of antibiotic-resistant bacterial infections which can be life-threatening. But bacteria are not the only cells capable of mutation. Cancer cells can do this too.

A study published in the journal *Science* shows that colorectal cancer cells mutate in response to targeted therapy. Targeted therapy is defined as treatment that is directed as a specific type of cancer or tumor, which is different from non-selective chemotherapy and radiation.

The sequence of events is familiar to anyone who has had a family member or close friend with cancer. A cancer patient is offered "gold standard" treatment, which "works" for a period of time. The reports are glowing – the tumor is shrinking, or the markers are getting lower and lower. Sometimes the patient is even declared cancer-free after completion of treatment. But eventually the cancer starts growing again and this time it does not respond to treatment, a phenomenon known as secondary resistance. Primary resistance is when the treatment does not work when used the first time. With secondary resistance, not only does the cancer come back, but it is often even more aggressive than it was before. Patients are typically weaker as a result of prior treatment, which lessens survival odds considerably.

In order to study this phenomenon, researchers treated colorectal cells with Erbitux (cetuximab), a monoclonal antibody treatment that binds to the epidermal growth factor receptors in order to stop cancer cells from proliferating. Erbitux is used to treat metastatic colorectal cancer, squamous cell cancer of the head and neck, non-small cell lung cancer, and squamous cell skin cancer.

In this study, most of the cancer cells died within 96 hours of treatment, but a small number of resistant cells survived. The resistant cells became sensitive when treatment resumed but after two weeks the cells developed permanent resistance.

The researchers identified the mechanisms of action. Treatment with Erbitux increased the proliferation of defective DNA polymerases, which are more apt to make mistakes while replicating, and at the same time decreased proliferation of corrective polymerases. Erbitux also increased markers of DNA damage and induced negative changes in the genome of the colorectal cancer cells, leading to more mutations and more genetic instability. In other words, cells became increasingly more damaged and unable to repair themselves. In fact, the cells' response to Erbitux was a stress response similar to the response that bacterial cells have to antibiotic treatment.[1]

Erbitux causes significant side effects when used to treat cancer in humans, which include rashes, generalized weakness, weight loss, diarrhea, nausea, vomiting, abdominal pain, constipation, low blood counts, difficulty breathing, cough, peripheral neuropathy, infection, liver damage, headache, insomnia, fever, chills, confusion, anxiety, depression, dehydration, and bone and joint pain.[2] This is a long list of side effects for a drug that only "works" temporarily, and sometimes not at all. In a Phase III Clinical Trial in which patients with metastatic colorectal cancer were randomized to Erbitux plus irinotecan vs irinotecan alone patients who took the combination including Erbitux showed some tumor reduction but overall survival was not improved.[3]

The same outcomes were reported in another trial in which 1630 patients with advanced colorectal cancer who had not previously received treatment were randomized to either chemotherapy alone or chemotherapy plus Erbitux. There was no increased survival time for the chemotherapy plus Erbitux group.[4]

The results are not much better for non-small cell lung cancer. When Erbitux was added to cisplatin and vinorelbine overall survival rate was increased by 1.2 months. In spite of these meager results, the researchers wrote, "Cetuximab added to a platinum-based chemotherapy sets a new standard for the first-line treatment of patients with non–small cell lung cancer."[5] The American Society of Clinical Oncology apparently agreed, stating in a press briefing that "these findings are likely to have a significant impact on the care of patients with these types of cancer."[6] Interesting statements in view of the fact that the drug had almost no impact at all – it was virtually useless.

The cost for this almost useless drug? In the U.S., 18 weeks of treatment with Erbitux costs an average of $80,000, more than the median annual household income for Americans. Based on clinical trial results, this means that it costs about $800,000 to prolong the life of one patient by just one year.[7]

These data reinforce the necessity of making InforMED decisions. In the case of cancer, patients are often rushed to drugs and procedures before they have any opportunity to look at outcomes data for proposed treatments, many of which, as this article shows, have little impact on survival, which should be the goal. In most cases, the best course of action for cancer patients is to take a few weeks to both calm down and thoroughly research their options before proceeding.

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[1] Russo M, Crasafulli G, Sogari A et al. "Adaptive mutability of colorectal cancers in response to targeted therapies." *Science* 2019 Nov;eeav 4474 DOI: 10.1126/science.aav4474

[2] http://chemocare.com/chemotherapy/drug-info/cetuximab.aspx

[3] Randomized Phase III Trial Showed ERBITUX® (Cetuximab) Significantly Improved Secondary Endpoints of Progression-Free Survival and Disease Control in Metastatic Colorectal Cancer Patients. Presented during the Annual Meeting of the American Association for Cancer Research. https://news.bms.com/press-release/randomized-phase-iii-trial-showed-erbitux-cetuximab-significantly-improved-secondary-e

[4] Maughan TS, Adams RA, Smith CG et al. "Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomized phase 3 MRC COIN trial." *Lancet* 2011 Jun'377(9783):2103-2114

[5] Pirker R, Pereira JR, Szczesna A et al. "Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomized phase III trial." *Lancet* 2009 May;373(9674):1525-1531

[6] ASCA Press Briefing Sunday June 1 9:00AM

[7] Cohen H> *Drug Topics Red Book 2008*, 2008112th edMontvale NJThomson Healthcare/Thomson PDR