WHEN FAILING CHEMOTHERAPY AND THE PHYSICIAN(S) SAY THERE IS NO MORE THEY CAN DO FOR YOU

From: https://www.pcf.org/c/when-treatment-stops-working-blame-resistance/

Targeted drugs. There are a few of these, and new compounds are being developed as we speak, in research funded by the PCF. Two of these are olaparib and rucaparib, approved by the FDA to treat ovarian cancer. The target of these drugs is pretty darn specific – a mutated BRCA Gene that is supposed to repair damage to DNA. Some men with prostate cancer have responded so well, Simons refers to them as "Lazarus patients." These are men with advanced metastatic disease, "with PSAs in the thousands, whose tumors are melting away." Mutated BRCA genes are the cause of breast cancer and other cancers, including prostate cancer, and they can be inherited. *Note: If cancer runs in your family, you should talk to your doctor about taking the new Cascade Genetic Test, a blood test that looks for 16 inherited genes found in different types of cancer; all of these genes are involved in DNA damage repair.*

How do they work? Olaparib and rucaparib are PARP-inhibitors. PARP is not a gene, but a protein that helps damaged cells repair themselves. *Cancers that spring from a damaged BRCA gene selectively use PARP as their repairman of choice. Without PARP to keep up the maintenance, the cancer cells die*.

These drugs are just the beginning. A bunch of genes involved in prostate cancer might make very effective targets – which means that if a genetic test shows that you have a mutated gene, there may be a medicine coming soon that will target that particular one.

"To have an extinction event, to cure men with advanced prostate cancer, we have to change the environment for the cancer cells," says Simons. "Our new cancer medications have to create an extinction event for which there is no countermeasure."

Immunotherapy. Toward this end, immunotherapy holds great promise. So far, drugs such as ipilimumab and pembrolizumab have worked only in a few men – but these men haven't just gotten a little bit better; they have shown spectacular improvement. Tumors and metastases in these "exceptional responders" have melted away.

These drugs, called checkpoint inhibitors, work by "waking up" the killer T cells – white blood cells that, if unleashed, can viciously attack and kill cancer cells. These cells typically don't do much good against prostate cancer because, early on, cancer cells put them in a straitjacket. Checkpoint inhibitors take the restraining bolts, or checkpoints, off of these T cells. "When the T cells wake up, they can multiply and destroy faster than cancer cells," Simons explains. "If you have thousands of T cells against a single prostate cancer cell, the cancer doesn't have time to mutate or hide; it's just eaten up."

Chemotherapy, when it works well, can do this, too, by a process of mass sterilization. Stem cells within the cancer can't replicate, and the cancer dies off. "It's like killing an entire squadron. The cancer cells can no longer replicate." Chemotherapy for prostate cancer is much more selective than it used to be; side effects are greatly reduced, and normal cells are left alone. "Amazingly, when this works, normal cells grow back in. If you kill the cancer cells, it doesn't leave a hole; your body will fill it in, just as if you've had surgery there. It does leave a Benign scar that you can see on a scan. But when immunotherapy works, it causes the body to reject cancer just as it would try to reject a foreign organ. We are just beginning to understand why some men are exceptional responders and others are not, and we are working to find ways to help more men become exceptional responders."

Roller coaster, or "bipolar" hormonal therapy. Another approach that has shown promise at Johns Hopkins is to make cancer cells extra sensitive by giving high-dose Testosterone after a course of ADT. "It's almost like they choke and die on a diet that's too rich after they've been starved. That is exploiting the understanding of stem cells."

Studying this "stemness" means learning where cancer cells are vulnerable – it's like the velociraptor testing the fences, except this time, we are the predator. "Cancers that kill have this

extraordinary property of renewal or evolution," says Simons. "A lot of our gene targets are these genes of evolution. Normal prostate cells don't evolve. They're the same as before. But the children of prostate cancer stem cells keep mutating. It's evolution within your own body." Prostate cancer stem cells are like dandelion seeds, he continues. "They're there, even if they haven't popped up yet." Finding a way to treat that one tiny, evolving bit of cancer, as soon as you see it – better yet, even earlier – may be the secret to extinction.

What can you do? One very important thing: *Donate to PCF*. Any donation you make, of any size, goes right to research. Two: *Talk to your doctor* about the state-of-the-art treatments you read about here, to see whether any are right for you. One reason that breast cancer treatment has made so much progress is that women have been their own advocates, and they have helped to drive the cure. Men with prostate cancer traditionally have not wanted to talk about it, have put off going to the doctor, and have not pushed for more answers. This needs to change, and it is changing. So, three: *Talk to other men about prostate cancer*. If they've never been screened and they're in their forties, encourage them to go. If they have cancer in their families, ask them to talk to their doctor about genetic testing.

Where are we headed?

Curing oligometastasis: Oligometastasis means you have just a few minuscule spots of cancer. "If you have only three or four bits of cancer and we can see all of them, we can give SBRT and cure the cancer that way," says Simons. Note: SBRT is stereotactic body radiation therapy, and its use here is different from its use as external-beam radiation therapy to kill the primary tumor in the prostate; instead of targeting the entire prostate, it is highly focused on areas just a few millimeters in diameter. This new use for SBRT is now possible because radiation is better, and so is imaging; now doctors can actually see these tiny spots soon after they develop, and go after them. Even a few years ago, this was not possible. Men with oligometastasis may not even need to start hormonal therapy.

Liquid Biopsy: We are getting much better at detecting circulating tumor cells (CTCs) in the bloodstream – before these cells ever set foot on a new territory and start to establish themselves. The next step after learning how to detect these cells reliably is learning how to treat them right there in the bloodstream. "That's how you treat HIV or tuberculosis or staph infection," says Simons. "You start treating based on a blood test, and you're treating when there are much smaller amounts of disease present."

Radiopharmaceuticals. Scientists in Germany, testing a nanoparticle technique developed at Johns Hopkins by scientist Martin Pomper, can kill individual prostate cancer cells with a fluorescent die that targets PSMA, prostate membrane-specific antigen, a protein that's only found on the surface of prostate and prostate cancer cells. An imaging technique, called PSMA Pet scan, is available at a few centers here in the U.S.

The bottom line: ***There is more hope now than ever.*** Doctors used to tell men with advanced prostate cancer, "The medicines stop working, but we don't know why." Now, we either *do* know why or *we are learning*. We now know that there are genetic differences – in cancer cells, in Hormonereceptors, in proteins on those cancer cells, in molecules on the surfaces of T cells, just to name a few. Every new bit of insight gives us a new target.

Terms to know from this article:

Tumor

A mass of excess tissue that results from abnormal cell division. Tumors perform no useful body function. They may be benign (not cancerous) or malignant (cancerous).

PSA

prostate-specific antigen (PSA): A substance produced by the prostate that may be found in an increased amount in the blood of men who have prostate cancer, benign prostatic hyperplasia, or infection or inflammation of the prostate.

BRCA

Are a human gene and its protein product, respectively. The official symbol (BRCA1, italic for the gene, nonitalic for the protein) and the official name (breast cancer 1).

Gene

The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

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Medical Oncologist Stephen Strum, a specialist specifically in research and treatment of prostate cancer, and particularly recurring/advanced prostate cancer since 1983 and considered one of the very top experts in such treatment, had the following to say to a patient's caregiver on the Physician to Patient (p2p) prostate cancer support list on 6/18/10 whose physicians had told the patient there was no more they could do for him:

Stephen Strum, MD> "You would need to work with a team to get clarification on much of the above issues as well as being caught up to date with his current tumor status and then to be presented with treatment options.

My recommendation would be for you to see if you are able to work with International Strategic Cancer Alliance (ISCA) based out of Philadelphia. First, check out the ISCA website at http://www.is-canceralliance.com/ . See if what they do resonates with your needs. I am now part of the ISCA team but it does involve many other experts in the field of oncology all over the USA and abroad. Then call ISCA and speak to Örn Adalsteinsson, Ph.D or one of his staff such as Fred Mills, who is a PC patient. If you are able to handle the finances then ISCA would proceed at least along the areas I have suggested." **(MY NOTE: Important to note "if you are able to handle the finances." In reviewing the above referenced URL it appears one's insurance may cover some part of treatment, but may not cover much other. Thus, one must be financially comfortable before considering this organization for comprehensive treatment).**

<Stephen Strum, MD> "I always recommend getting an appraisal of STATUS before talking STRATEGY. I have no idea of the dosing of Taxotere or whether or not your husband has neuroendocrine (NE) PC which is sensitive to certain kinds of chemo.

In addition, there are some treatments that appear very promising that can be looked into:

Novel Therapies of Prescription Agents (Clinical Trial Status)

AR inhibitors: Abiraterone, MDV3100
VEGF-R inhibitors: sorafenib, sunitinib, cediranib
Epothilones: patupilone, Ixabepilone
Cytoprotective chaperone inhibitors: OGX-011 Arginine deiminase (ADI)
Apoptone AR decoy molecules Denosumab Dolastatins Ipilimumab (MDX-010)
Oncolytic Virus Rx PARP inhibitors

And, there are other treatments that may be considered

Novel Therapies of Natural Agents

2-deoxyglucose
3-bromopyruvate
DCA (dichloroacetate)
Digitalis & other cardiac glycosides
Flufenamic acid
Flurbiprofen
GcMAF
Honokiol
HIV protease inhibitors
ActivAmune (DIM)
Noscapine
Phenylbutyrate
Salinomycin
Ursolic Acid

Navigating the medical waters full of bureaucracy is overwhelming.
Here is where an organization like ISCA should be able to part the waters for you.
But again, a full status appraisal is the first priority."