

New HOPE for Adrenal Cancer

Despite some disappointing studies, researchers pursue IGF2 and other suspects for drug targets

By John Bohannon, PhD

Most cancers are neighborhood bullies, stealing blood and pushing into the surrounding tissues. Unless a tumor compromises a vital organ, people can live for years, sometimes a lifetime, with cancer as a passenger. But cancers that take root in the endocrine system are terrorists. Even a tiny group of cells overproducing hormones can throw the rest of the body into chaos. And adrenal cancer is one of the worst.

It is a rare disease, striking about one in a million people each year, but adrenal cancer is one of the most deadly. Like most rare diseases, adrenal cancer treatment was hampered by a lack of government funding, industry interest, and the basic challenge of having so few patients to study. But the adrenal cancer community of researchers and patients pulled together, sharing their data and resources.

“The patient groups have galvanized and that has made all the difference,” says Gary Hammer, an adrenal cancer researcher at the University of Michigan and an Endocrine Society ambassador.

One crucial insight has come from Brazil where adrenal cancer rates are more than 10 times higher than the rest of the world. A mutation responsible for this boost has been spotted, and that is shining new light on the inner workings of the disease. (See sidebar.)

Chasing an Orphan

The adrenal glands look like a pair of hats worn by the kidneys. Among their many jobs, they are best known for marshalling the body’s “fight or flight” response by releasing adrenalin into the bloodstream. But they also produce cortisol in response to stress, aldosterone to regulate kidney function, and androgens for developing and maintaining male and female sex traits. Different cells

ADRENAL Roles

- Marshall the body’s “fight or flight” response by releasing adrenalin.
- Produce cortisol in response to stress.
- Produce aldosterone to regulate kidney function.
- Produce androgens for developing and maintaining sex traits.

AT-A-GLANCE:

- Adrenal cancer patient groups and researchers pull together to advocate for treatment.
- When cancer takes root in the adrenal gland, it becomes a lottery of terrible symptoms.
- Researchers are studying insulin-like growth factor 2 (IGF2), β -Catenin, and p53 for potential drug treatments.

within the adrenal gland are responsible for producing each hormone. So when cancer takes root in the adrenal gland, it becomes a lottery of terrible symptoms.

One of the most bizarre outcomes is a sudden outward sex change if androgen levels go off kilter. Both young girls and adult women can suffer virilization, sprouting hair all over their bodies. Boys and men can feminize, growing breasts. If an adrenal cancer overproduces cortisol, the body blows up with fat in strange places. Pads of fat form on the back of the neck like a water buffalo, and the face can swell into a moon. If aldosterone is overproduced, blood pressure goes through the roof.

Having any of these symptoms can be a life-saver for adrenal cancer victims, because they can lead to a quick diagnosis. "But for the rest, it's pretty horrible," says Pierre Val, an endocrinologist who studies adrenal cancer at Clermont University in Aubiere, France. "The unlucky ones just suffer from a diffuse, nonspecific body pain. By the time it is found, the tumor can sometimes be as large as 2 or 3 kilograms. That is so enormous that they often have digestive trouble. By then there is usually nothing to be done for them."

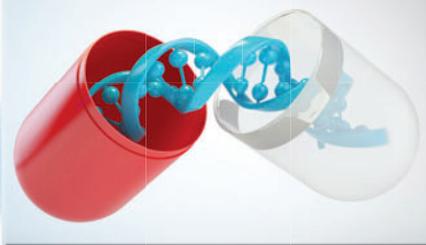
Catching adrenal cancer is among the most aggressive. The adrenal glands have direct access to the heart via the vena cava, so metastatic adrenal cancer cells have a superhighway for reaching the rest of the body. The best way to survive is early diagnosis and surgery.

Pursuing Badly Needed Drugs

But not all adrenal cancer patients are good candidates for surgery. For some, the only option is chemotherapy and a drug called mitotane, the only proven adrenal cancer drug on the shelf. "Mitotane is very toxic," laments Val. "It's a pesticide, a derivative of DDT, and it must be taken orally." The side effects are miserable. And what's

Few DRUG Therapies

Mitotane is currently the only proven adrenal cancer drug on the shelf. However, several small biotech companies have new drugs in development for adrenal cancer, including Atterocor, which should be in phase 1 trials later this year.



worse, it is only barely effective. "A big international trial of chemotherapy and mitotane was published a few years ago. From a scientific point of view, it was pretty scary to see that the efficacy is pretty minor," he says. "You only get about five months of protection and then usually a relapse with a more aggressive tumor."

This is why new drug targets are so badly needed for adrenal cancer. But the hunt for them has really only picked up pace over the

past decade, says Hammer. The main challenge has been the small number of patients. "Until recently, for doctors who saw adrenal cancer it would be the only one they would see in their career." For so-called orphan diseases like these, the motivation just isn't there to spur government research funding or pharmaceutical industry investment.

But over the past decade, the community of adrenal cancer researchers, doctors, and patients has turned their situation upside down. Doctors and patients slashed through red tape to make adrenal tumor samples available for research. Centers of excellence for adrenal cancer treatment have popped up at the University of Michigan, Paris, and elsewhere. And perhaps the biggest coup came last year when the Cancer Genome Atlas chose adrenal cancer as its first rare cancer to sequence. Today adrenal cancer is considered a success story among orphan diseases.

Nonetheless, Val expects a long uphill battle. What is known so far is that several genetic changes occur in adrenal cells before they

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— Martin Fassnacht, an adrenal cancer researcher at the University of Munich in Germany



The American Cancer Society estimates approximately 300 adrenal cancer cases each year. "The average age of those found with adrenal cancer is around 45 to 50, but it can happen at any age, even in children. It seems to occur more often in women," according to the American Cancer Society.

Mutation Responsible for MUCH HIGHER ADRENAL CANCER RATES IN BRAZIL

When Ana Claudia Latronica was a PhD student studying adrenal cancer in Brazil in the 1990s, the disease was shrouded in mystery. Adrenal cancer tends to hit people either in childhood or later as adults. The rate of childhood adrenal cancer in southern

Brazil is more than 10 times higher than the rest of the world.

“We thought that a potential environmental factor could be implicated,” says Latronica. But the picture changed dramatically when a single mutation was found to be responsible.

Based on population genetics, the mutation seems to have appeared in native populations of southern Brazil about 10,000 years ago. It has stuck around ever since. And the gene that is changed by the mutation is p53, a classic cancer gene.

Latronica was hooked. After finishing her PhD in 1995, she dove into clinical research on adrenal cancer and never looked back. The hope is that some combination of

therapies that target p53 and the other genes known to be involved will save patients from what is usually unavoidable death.

For now, early detection offers the best chance of survival. “The population is aware about the high prevalence of adrenal cancer,” says Latronica. “There is an obligatory neonatal genetic test available in the state of Parana. This test is a very controversial issue,” she notes. Diagnosing adrenal cancer in children is relatively easy, since it often causes such dramatic problems due to hormonal imbalances. Meanwhile, not everyone who carries the mutation develops the cancer. Revealing the mutation can “sometimes cause panic or serious problems in these families,” she says.



become cancerous. “We see the same mutations popping up,” says Hammer. That indicates that there is a common set of pathways that new drugs might target.

The three main suspects are insulin-like growth factor 2 (IGF2), β -Catenin, and p53. Both Val and Hammer have been focusing on untangling the roles that these genes play in the disease, and focusing particularly on IGF2 as a drug target. “IGF inhibitors already exist,” says Hammer. “They’ve just been waiting for a disease to treat.” Last summer, Val and Hammer published their results within weeks of each other.

“It was a terrible disappointment,” says Val. Neither study found that inhibiting IGF2 could stop adrenal cancer’s progression. “We were all hopeful, but it’s clear that controlling IGF2 alone will not be the cure.” However, it is clearly involved, and it may be more important in a subset of adrenal cancers. “I am not yet convinced that the IGF story is dead,” says Martin Fassnacht, an adrenal cancer researcher at the University of Munich in Germany. “We have here two patients who have a dramatic partial response [to an IGF inhibitor].” It could be just a stroke of rare good luck for these patients. “However, I am personally quite convinced that it is related to the IGF inhibitor,” he says.

The pharmaceutical industry isn’t sitting on its hands. Several small biotech companies have new drugs in development for adrenal cancer. One was started by Hammer called Atterocor hopes to be in phase 1 trials later this year.

Even without a cure yet in sight, researchers are giving hope for adrenal cancer patients. “The only way to make progress is to work together to understand the biology of the disease,” says Hammer. “We have to work together.” **EN**

—Bohannon is a freelance writer in Boston, and a regular contributor to Endocrine News.

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