Our milestones: the birth of a new prostate cancer drug

Category: Science blog **September 21, 2015** Henry Scowcroft2 comments

This entry is part 24 of 25 in the series Our milestones

In the latest in Our milestones, we look back to the 1990s, and to our 'first-in-man' trial of prostate cancer drug abiraterone – a vital step in the drug's development that set the scene for its progression through to routine use on the NHS.

"The mid-90s was a dark time for prostate cancer trials," recalls Cancer Research UK's expert Professor Malcolm Mason. "The disease had a much lower profile, and we only had limited tools to help men with advanced disease: hormone therapy, and radiotherapy to control pain and other symptoms.

"Things like chemotherapy weren't really taken seriously", he says, "as the limited clinical evidence we had led us to think it wouldn't make much of a difference when the disease had already spread".

The situation got worse when a large UK prostate cancer trial failed to recruit enough patients: "We were very disheartened. The generally accepted view was that there wasn't much point in setting up more," he recalls.

Today, this picture is almost unrecognisable, with several new treatments now available, together with a new optimism in the field.

But how did we get here? In this blog post, we'll look at how – thanks to research – that picture began to change, and how the outlook for men with the disease is now improving year on year.

A new dawn

Prostate cancer is the most common cancer among UK men, affecting nearly 42,000 each year. And although it can be cured if diagnosed early, the picture changes if it starts to spread.

Since the 1940s, the mainstay for treatment for men with advanced prostate cancer has been to block the action of their male sex hormones (collectively called 'androgens') – so-called androgen deprivation therapy – halting the disease in its tracks.

But after months or years, the cancer almost inevitably starts growing again. And from there, things generally only have one outcome.

At the beginning of the 1990s, however, UK scientists started to become more optimistic. There was a new dawn in understanding hormone biology, and the molecules involved in hormone-linked prostate cancer growth were being isolated and understood.

And at our Cancer Therapeutics Unit at London's Institute of Cancer Research (ICR), a team led by Professor Mike Jarman and Elaine Barrie were developing drugs to try to shut down the production of the hormones that fuel prostate cancer's growth, rather than merely block their action.

And they were zeroing in on a promising-looking compound: **abiraterone acetate**.

From bench to bedside

By the mid-90s, Jarman, Barrie and their colleagues had proven that abiraterone worked in cancer cells in the lab, and then in animals with prostate cancer – a story we've detailed previously.

It was time for the crucial test – to see if the drug could shut off testosterone production in patients. Through the Cancer Research UK Centre for Drug Development (formerly our Drug Development Office), a small series of trials was conducted at several hospitals, led by Professor Ian Judson at the Royal Marsden in London.

Judson recalls: "We were looking to see if we could either completely suppress hormone levels in men who hadn't begun treatment yet, or have an extra effect, over and above current hormone drugs, in men who were currently being treated."

"It was a simple but absolutely vital study" – *Professor Malcolm Mason*

“It was a very simple but absolutely vital study,” says Mason, whose patients at Cardiff’s Velindre Cancer Centre took part in the trial. “Our idea was to see if a single tablet of abiraterone could produce the sort of impact that the lab studies suggested it should.”

It was a classic example of a ‘phase I’ trial – the search for simple answers to fundamental biological questions. Does this drug do what we think it should? At what dose? And – just as important – does it do anything we didn’t anticipate?

Over six months in the late 90s, Judson, Mason and their team recruited 26 volunteers with early-stage prostate cancer, who were either waiting for surgery to remove their cancer, or having hormone treatment.

At first, men on hormone treatment received a single dose of abiraterone, and over the next few days, gave blood samples to see what happened to their hormone levels.

Ultimately, they found that a 500mg dose of abiraterone could indeed reduce a man’s androgen levels to unprecedented lows, for several days, without any short term side-effects.

“It worked exactly as we expected,” says Mason.

Over the next few months the team carried out further studies, to see what happened in men with normal androgen levels given the drug for 12 days. Although things were slightly less clear cut, the hormone levels fell in these men too.

But when the trial team convened to what to do next, the story took an unexpected step backwards.

Back on the shelf

“We had a teleconference to decide what to do,” recalls Mason. “And we really struggled to come to any sort of conclusion.”

The issue was not that the drug worked: it was who to give it to.

“We couldn’t agree on who would benefit most,” says Mason. “Should we give it early on? Or as a first line hormone therapy? Or after current hormone treatments? It wasn’t clear cut, and we couldn’t agree.”

This dilemma was because, at that time, no-one really understood exactly how hormones fuelled prostate cancer.

Mason explains: “About 90 per cent of a man’s testosterone is produced by his testicles. But as researchers in the late 80s had worked out, the rest is produced by various other tissues – notably the adrenal glands.

“And at that time we already used a combination of drugs, which suppressed both testosterone production by the testicles, and also the extra 10 per cent of testosterone produced elsewhere. We rather optimistically called this ‘Maximal Androgen Blockade’”.

They saw it as old-hat. No-one wanted an ‘old-fashioned’ hormone blocker.

– Prof Ian Judson

“But the extra gain in survival with this combination, compared with suppressing testicular testosterone alone, was very small. So we wondered how a single drug that effectively did the same as this combination, would give any greater benefit than what we had already.”

On top of this, drug companies weren’t terribly interested in the idea. “They saw it as old-hat: yesterday’s chemistry, yesterday’s drugs”, recalls Judson. “The flavour of the month was so-called ‘targeted’ therapy, aimed precisely at genetic faults in cancer.

“No-one wanted an ‘old-fashioned’ hormone blocker.”

This attitude was reflected in the struggle to get the trial results published. “I’ve still got a rejection letter in a box file somewhere,” says Judson. “The reviewers asked, ‘Why would anyone think that further suppression of testosterone would be effective in prostate cancer that has already become resistant?’”

Abiraterone’s development ground to a halt, and the trial data were not to surface until 2004, when the paper was finally published in the British Journal of Cancer.

“This was because we were lacking what, in retrospect, was a crucial piece of biological information – something that wouldn’t be uncovered for a few more years,” Mason says.

This was the discovery, in the early 2000s in US laboratories, that as prostate cancers grow, they can acquire a new trick: **they begin producing *their own* testosterone**.

And this allows them to fuel their own growth, even in the presence of hormone-blocking drugs.

“It was a game-changer,” recalls Mason.

Sex addicts

Before this discovery, when a man’s prostate cancer had come back after hormone treatment, it was said to be “hormone-independent” (or, hormone-‘resistant’) – the cancer no longer seemed to rely on hormones to grow.

This had been shown to be completely wrong. “Far from being hormone-‘resistant’, these prostate tumours are *completely addicted* to male sex hormones,” says Mason.

The ‘resistance’ theory had been turned on its head.

In characteristic dry, scientific fashion, the conclusion of one these research papers reads:

> **New agents that target androgen receptor directly, and prevent formation of androgens within prostate cancer tissue, may offer the most effective approach to prolong remission of recurrent prostate cancer.**

In other words, the discovery signalled clearly that drugs designed to directly shut off hormone production could prove highly effective.

Abiraterone, languishing at the back of a dusty shelf in The ICR, was back in the spotlight.

Rapid process

Armed with the knowledge that abiraterone could target these addicted prostate cancer cells, the drug gained a new lease of life.

Through Cancer Research UK’s commercial arm, Cancer Research Technology, the rights to develop the drug were licensed to pharmaceutical company Cougar Biotherapeutics (now part of Janssen Pharmaceuticals).

The rest is history: with backing from Cougar, The ICR’s Professor Johann de Bono spearheaded the clinical trials in the 2000s and 2010s, proving it could extend men’s life for vital months after hormone therapy and chemotherapy.

In late 2012, it was finally approved for use across the NHS for treating these men. And in 2016, it was approved by NICE for use before chemotherapy, making it availabe to even more men.

“Today, abiraterone is incredibly important for patients with advanced prostate cancer and their families,” said de Bono, who is now, with support from Cancer Research UK and others, trialling abiraterone in combination with other drugs. “We at the ICR are proud to have led its development.”

But none of this would have been possible without that early Cancer Research UK-funded ‘first-in-man’ study in the mid 90s. “It was a pivotal trial, and laid the foundations for everything that happened subsequently,” says Mason.

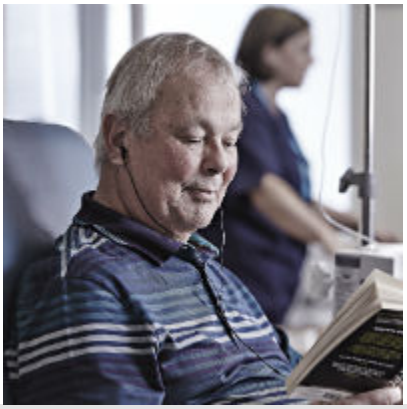
It’s also a salient example of why laboratory research is fundamental to the success of clinical studies, and why we are so passionate about funding and integrating both types of research.

Winning combinations

So what next for abiraterone?

It’s not a cure for prostate cancer. But in combination with other drugs, it’s starting to turn the tables on the disease. Alan is 72, and is now on his third prostate cancer trial, having first been diagnosed back in 2005.

He’s been treated with surgery, chemotherapy, radiotherapy and hormone therapy. And, in May last year, he enrolled on a phase I trial of abiraterone – this time in combination with another drug developed by Cancer Research UK-funded scientists: olaparib.



“My energy levels and general well-being have been good since I started on the trial” – *Alan*

“Since starting on this trial my PSA level has to-date dropped by half – so I certainly think that this combination of drugs is doing some good work,” he told us. “I’m feeling fine. My energy levels and general well-being have been good since I started on the trial, and I haven’t had any side effects at all.”

Alan – a grandfather of four – acknowledges that it is hard to ascribe the benefits to any particular part of the treatment (as part of his treatment he’s also taking the steroid prednisolone). But at 72, ten years after his diagnosis, he’s still walking the dogs and playing golf three times a week, “weather permitting”.

And abiraterone’s not the only new kid on the block – in 2013 another hormone-targeting drug, enzalutamide, was also licensed for use. So the challenge in the immediate future is to work out how best to use these new drugs – at what stage, in what order, or which combination (something our STAMPEDE trial is now focusing on).

“It’s a far cry from the pessimism of the 90s,” says Professor Mason. “The huge leap forward in our understanding of the disease has turned into a series of new drugs, and we’re finally seeing the sort of progress in prostate cancer that other cancers have seen in recent decades.”

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