HEALTH

Jill Margo: jmargo@afr.com

SOMETHING OLD, SOMETHING NEW

An experimental new treatment uses out-of-patent drugs to enhance standard cancer therapies, writes **Jill Margo**.

On his two-hour train ride home from London every evening, Dr Samir Agrawal goes through the accumulated emails of the day. By the time he gets to his station in Kent, he's usually cleared them. But one email kept surviving the routine cull.

It was an invitation to join a medical group that appeared to have a new way of boosting conventional treatment for cancer. It had a hint of alternative medicine about it and, as a cancer specialist at St Bartholomew's Hospital and a senior lecturer at Queen Mary University of London, he wasn't about to stray out of the mainstream.

But his curiosity was aroused and he explored the scientific literature behind it. The more he read, the more promising it seemed.

"What I saw was something that was novel and, in some ways, completely old," says Agrawal.

Dr Samir Agrawal is a cancer specialist at St Bartholomew's Hospital in London. PHOTO: LOUISE KENNERLEY

It was old because it used a clever combination of four old licensed drugs – all out of patent – to enhance standard treatments used for various forms of cancer.

These were well known, non-cancer drugs that happened to have some cancer-fighting properties.

That regular drugs can also have anti-cancer properties is not unusual. "In our current pharmacopoeia, there are 70 to 80 licensed, non-cancer drugs that have some scientific evidence for efficacy in cancer," says Agrawal.

During their own research, some patients come across these drugs and take them at random, in the hope they'll help. This is not advisable.

But with this new approach, which is experimental rather than alternative, just four (later five) of these drugs were given under strict supervision.

We hope to show there is a clear positive signal to support this combination of drugs becoming mainstream.
Dr Samir Agrawal

They had been carefully selected for their combined ability to weaken cancer cells so that traditional treatments, such as chemotherapy, could be more effective.

"This seemed a positive thing to offer to patients, because there was no way they would be able to access this kind of treatment through our National Health Service, where we have set protocols," says Agrawal.

When he went to talk to Care Oncology Clinic (COC), which delivers the therapy in London, the discussions were frank.

"We discussed the challenges and the reputational risks," says Agrawal. "I could see how some of my colleagues would perceive this negatively, regarding it as alternative, as well as being offered in the private sector. They might think desperate patients were being commercially exploited.

"But the therapy is not available on the NHS [the UK's National Health Service] and the fees are modest."

Impressed, Agrawal joined COC part-time. That was five years ago, and today he says there is more acceptance of the therapy. It helps that similar therapy is being studied at major cancer centres in the US, Europe and Sweden.

While there is no proof yet, there are some early signals it may work. Agrawal is lead investigator of the COC trial, which has two components – a retrospective part that is currently underway, and a prospective part that is awaiting funding.

"While it is too early to report from the retrospective study, there is a clear signal coming through from patients with aggressive brain cancer, glioblastoma.

"With the best standard of care, their overall median survival is usually 15 months," says Agrawal. "We have analysed 100 such patients who received our therapy and published preliminary data in the *Frontiers in Pharmacology* journal. The therapy was well tolerated; 85 per cent took all four drugs and there were no significant side effects. With many caveats, their median overall survival is 27 months. So, it looks encouraging."

But how does it work?

"The science behind these drugs is extensive. A large number of laboratory studies show they help to impair metabolism – in other words, they impair the way cancer cells use energy.

"Sugars and fats drive the metabolic process. Within cells, these nutrients are converted into a form of energy to allow the cell function, just like power stations turn coal into electricity.

"We use these four drugs to try to block this conversion. Often, if we block one line, cancer cells smartly find a way around it, so we try to block various lines by using a combination of drugs."

While agents like chemotherapy aim to break the cell's DNA, these drugs aim to starve the cell of the energy to repair the DNA and reproduce.

So, what drugs are used? One is metformin, a diabetic drug that reduces both sugar levels in the body and the cell's capacity to grab sugar from the environment.

The other drugs used to disrupt the energy conversion process are Atorvastatin, an anti-cholesterol drug; mebendazole, an anti-parasitic drug; and doxycycline, a common antibiotic.

More recently, Flarin, a non-steroidal anti-inflammatory, has been added. Inflammation is prominent in cancer, and this drug inhibits a protein that helps cells repair themselves.

Agrawal, a specialist haemato-oncologist, was in Australia this month to address the World Congress of Intensive Care, annual mycology meetings and to talk at various hospitals about cancer patients' susceptibility to life-threatening infections.

He told of a new cancer patient, a doctor. Her husband was a doctor too and they came into COC fully informed of the science.

"Her basic premise was that she failed to see what harm this could do," says Agrawal. "If the harm was very little and the potential gain may be significant, why not!"

After a £450 ($845) enrolment fee, she would have paid £220 for the cost of the five drugs for a quarter, plus £200 for a quarterly consultation with access to a 24-hour helpline.

The COC protocol aims to slow the progression of cancer and also treats people with cancer who are not currently on any standard treatment. "We hope to show there is a clear positive signal to support this combination of drugs becoming mainstream," he says.

This approach is not available in Australia. "Off-label use of medicines for cancer should be used on an ethically approved clinical trial protocol," says Professor Grant McArthur, head the Molecular Oncology Laboratory at the Peter MacCallum Cancer Centre.

Other cancer experts expressed some scepticism and were reluctant to comment.

Jill Margo is an adjunct associate professor at the University of NSW, Sydney

Care Oncology Clinic i London har sammensat COC Protokollen som har vist gode effekter på de fleste kræfttyper. Især Glioblastom har vist, i et studie, at Protokollen har stor effekt og fordoblet overlevelsestiden fra ca. 14 måneder til ca. 35 måneder - en fordobling som ikke ses med andre behandlinger.

COC Protokollen tages komplementært til den almindelige standardbehandling og booster denne således at både overlevelse oftest forlænges betydeligt og der opnås en kræftfri tilstand hurtigere end uden Protokollen.

COC Protokollen bliver udskrevet af COC i London, enten via en online web konsultation eller en konsultation i klinikken for dem der kan og gerne vil have fysisk kontakt med lægerne i London. COC udleverer en recept som indtil 31. december 2020 er gældende i Danmark og danske apoteker skál udskrive lægemidlerne på recepten. Det er også muligt - ganske svært men muligt - at få udskrevet de fire lægemidler i Protokollen gennem en dansk praktiserende læge. Dette oplever vi dog som meget svært.

FOOKiD har gennem lang tid forsøgt at få danske praktiserende læger til at forstå Repurposed Drugs og dermed COC Protokollen men indtil nu har vi kun haft ganske lidt held med denne påvirkning. Dog kan vi snart oplyse om en dansk klinik som meget gerne vil samarbejde med COC i London og dermed udskrive COC Protokollen i Danmark.