SCIENCE

Prof Jimmy So (at right) and Dr Yong Wei Peng (far left) have been using the Pressurised Intraperitoneal Aerosol Chemotherapy or Pipac method since December 2016. With them is Dr Kim Guowei, who is one of the clinicians involved in the studies, and among the surgeons who can perform Pipac procedures. PHOTO: LIANHE ZAOBAO

Local scientists here have been testing different methods of detecting and treating various types of cancer. The Straits Times looks at some of their research findings.

New chemotherapy option for those with late-stage cancers

Colon, gastric, ovarian cancer patients may benefit from drugs delivered in aerosol form

Cheryl Tan

A targeted method of administering chemotherapy drugs to patients with colon, gastric and ovarian cancers could potentially bring hope to those who are in the late stages of their ailment.

The Pressurised Intraperitoneal Aerosol Chemotherapy (Pipac) method distributes drugs in aerosol form – through a device called a port – directly into the abdomen via keyhole surgery.

The technique, which has fewer side effects compared with conventional chemotherapy, has been successfully introduced at the National University Hospital (NUH) and National University Cancer Institute, Singapore (NCIS).

Professor Jimmy So, head and senior consultant with NUH's division of general surgery (upper gastrointestinal surgery), has been using the method with Dr Yong Wei Peng since December 2016.

The latter is a senior consultant with the department of haematology-oncology at NCIS.

A total of 49 Pipac procedures have been administered to 31 patients so far, with the majority afflicted with gastric or colorectal cancer.

Around 60 per cent of patients saw their tumours shrink in size. But for many, the cancer had already spread to other organs, and they were unresponsive to the treatment, especially since they were in the late or final stages of the disease, noted Prof So.

There were two cases of mild pancreatitis among the patients but no deaths.

Prof So said that at the advanced stage, the cancer often spreads to the peritoneal cavity, which is a space within the abdomen that contains organs such as the stomach and liver.

This tends to produce excess fluid in the abdomen, causing significant bloating and intestinal obstruction, which can be extremely uncomfortable for the patient.

The Pipac method sees the chemotherapy solution converted into fine aerosol droplets before they are distributed more evenly in the peritoneum cavity and more deeply into the cancer cells.

"Smaller amounts of the chemotherapy drug can be administered since it directly targets the affected area, which means that very little of it will be absorbed into the bloodstream, thus reducing the side effects," said Prof So.

On average, around 3,000 new patients are diagnosed with the three cancers each year, with around 30 per cent showing spread to the peritoneal cavity.

The three cancers are among the leading causes of cancer-related death in Singapore.

The Pipac method is performed as a short and minimally invasive keyhole procedure.

The chemotherapy is administered as fine air droplets by a micro-pump into the peritoneal cavity under gentle pressure for around 30 minutes.

The procedure is done under general anaesthesia, with continuous real-time video monitoring within the abdomen.

Ideally, the patients should undergo at least three rounds of treatment to see effective results, said Dr Yong.

"Pipac is well-tolerated and tumour regression was observed in patients receiving at least two Pipac procedures.

"The encouraging result has led to the development of Pipac with immunotherapy in a new study," he added.

NUH is currently leading a new international clinical trial which combines the Pipac treatment with immunotherapy for stomach cancer patients who have seen the ailment spread to their peritoneum.

Prof So hopes that the trial can soon be extended to patients who are at an earlier stage of cancer so that the treatment can be more effective for them.

He noted that some international trials – which involved patients with early-stage cancers – had seen a clinical response rate of up to 80 per cent or 90 per cent.

Currently, NUH is the main training centre for Pipac procedures in Asia, transferring the skills to more than 140 clinicians from 28 countries around the world.

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FEWER SIDE EFFECTS

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PROFESSOR JIMMY SO, head and senior consultant with the National University Hospital's division of general surgery (upper gastrointestinal surgery).

ENCOURAGING RESULT

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DR YONG WEI PENG, senior consultant with the department of haematology-oncology at the National University Cancer Institute, Singapore.

Scientists here find way to improve outcome for breast cancer patients

Local scientists have discovered a way to use an alternative drug to counter resistance to a form of targeted therapy used to treat patients with HER2-positive breast cancer.

Drugs often used to treat patients with this condition may stop working after some time, causing a relapse.

Researchers from the Cancer Science Institute of Singapore at the National University of Singapore, the Genome Institute of Singapore (GIS) under the Agency for Science, Technology and Research, and the National University Cancer Institute, Singapore (NCIS), together with their international research collaborators in Denmark, have looked into why this happens.

The team, led by Professor Lee Soon Chin from the Cancer Science Institute and Professor Yu Qiang from GIS, focused on a protein called the HER2 (human epidermal growth factor receptor 2), which stimulates cancerous growth of breast cells when present in excessive amounts.

To decipher the resistance mechanisms of the cancer to the anti-HER2 therapy, the team used existing data from a biochemical database along with tumour samples from 29 patients enrolled in a clinical trial at NCIS.

Drugs that targeted the HER2 protein often became ineffective eventually, though scientists were unable to figure out why.

To decipher the resistance mechanisms of the cancer to anti-HER2 therapy, the team used existing data from a biochemical database, along with tumour samples from 29 patients enrolled in a clinical trial at NCIS.

They zeroed in on an enzyme sub-unit, known as PPP2R2B, which suppresses cancer by making chemical modifications in a signalling pathway.

Breast cancers that did not respond well to anti-HER2 therapy tended to have lower levels of the PPP2R2B enzyme.

The activity of the PPP2R2B enzyme was, in fact, suppressed by another enzyme, known as EZH2.

The researchers plan to conduct a clinical trial to test the efficacy of combining both drugs to treat patients with HER2-positive breast cancer.

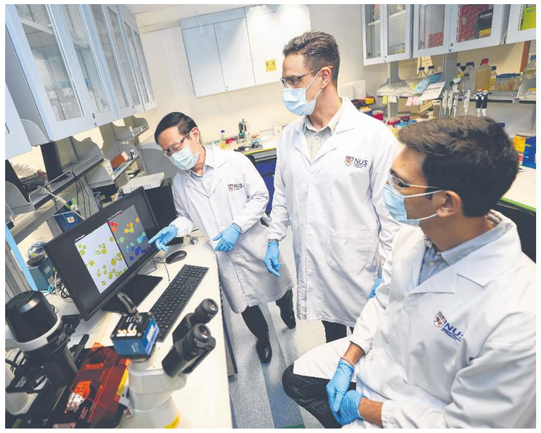
In addition, the PPP2R2B enzyme could be used as a potential predictive marker to identify patients who may potentially be resistant to standard anti-HER2 therapy and may benefit from additional therapy.

Prof Lee, who is also head and senior consultant at the Department of Haematology-Oncology at NCIS, said that HER2-positive breast cancer makes up 20 per cent to 25 per cent of all breast cancers.

"Despite initial effectiveness, resistance to anti-HER2 therapy develops almost invariably in patients with advanced cancer, and they will eventually succumb to the disease," she noted.

"This study provides insights into why anti-HER2 drugs eventually fail and offers a solution to restore sensitivity to anti-HER2 treatment, which may prolong the survival of patients."

Cheryl Tan



National University of Singapore researchers (from left) Lim Chwee Teck, Yuri Belotti and Jokhun Doorgesh Sharma demonstrating how the AI-based algorithm differentiates cancer cells based on their acidic fingerprints. ST PHOTO: TIMOTHY DAVID

NUS researchers tap AI to determine acidity of cancer cells

National University of Singapore (NUS) researchers can now identify cancer cells by studying their acidity or pH levels using artificial intelligence (AI) technology.

This technique could be potentially useful in detecting cancer cells in tissue samples, obtained from either tumour biopsies or liquid biopsies, which are blood tests.

"As the number of cells in these samples can be in millions or even billions, the ability to detect the very few cancer cells among the others will be useful for clinicians," said Professor Lim Chwee Teck, director of the Institute for Health Innovation and Technology (iHealthtech) at NUS.

The living cells are first coated with a layer of bromothymol blue, a pH-sensitive dye that changes colour according to acidity levels.

Due to its intracellular activity, each type of cell displays its own "fingerprint", which consists of a unique combination of red, green and blue (RGB) components when it is illuminated.

Cancer cells have an altered pH, resulting in lower acidic levels. This means that the cells react differently to the dye, which leads to different RGB fingerprints.

These fingerprints are then captured using a microscope equipped with a digital colour camera.

Using an AI-based algorithm, thousands of cells originating from the same tissue can then be imaged and classified into normal or cancer cells.

Each cancer test can be completed in under 35 minutes, and each cell can be classified with an accuracy rate of more than 95 per cent.

The research findings were published in the scientific journal APL Bioengineering on March 16.

"This demonstrates the potential of our technique to be used as a fast, inexpensive and accurate tool for cancer diagnosis," said Prof Lim, who led the research study.

The researchers also extended their analysis to differentiate between benign and metastatic cancer cell lines.

They investigated four different cell types: normal cells, benign breast tumour cells, breast cancer cells and pancreatic cancer cells.

These cells were identified and classified with an accuracy rate of 93 per cent, said Dr Yuri Belotti, research fellow at iHealthtech.

He added that the accuracy rate of the algorithm depends on how different the cellular RGB fingerprints are from one another, and the number of cells the AI algorithm learns to identify.

More importantly, using this technique can keep the cancer cells alive, so that clinicians can culture them for drug tests in future, said Prof Lim.

Current imaging techniques often require elaborate cell preparation steps, and often induce toxic effects on the cells, eventually killing them.

The team envisions a real-time diagnostic technique where clinicians are able to diagnose cancer at any stage based on the sample obtained from a blood test.

"Our previous studies had shown that the number of circulating tumour cells obtained from a blood draw does correlate with the (patient's) stage of cancer.

"So we hope to be able to detect and ascertain this number of circulating tumour cells and even their malignancies by performing cell-by-cell imaging and analysis as they flow through a channel in a microfluidic chip," said Prof Lim.

This can be extended to monitor cancer progression, effectiveness of a treatment, and even alerting on the risk of a relapse after a successful treatment, he added.

Cheryl Tan

STUDYING TUMOUR CELLS

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PROFESSOR LIM CHWEE TECK, director of the Institute for Health Innovation and Technology at NUS.

ScienceTalk

Cancer patients' Covid-19 dilemma – to jab or not to jab

Wong Seng Weng
For The Straits Times

These days, many of my cancer patients are engaged in a soliloquy much like Shakespeare's Hamlet: To be, or not to be.

In their case, they ask: to jab, or not to jab?

Cancer patients are agonising over whether or not to receive the Covid-19 vaccine.

These patients are especially vulnerable to the deadly virus.

Multiple reports in medical literature have documented a higher infection risk as well as probability of developing complications and of mortality in such patients.

Depending on which specific report one is looking at, the mortality rate in cancer patients who came down with Covid-19 ranges from 5 per cent to 60 per cent, with the median hovering at about 25 per cent.

In comparison, the mortality rate of those in the general population who contract Covid-19 is 2 per cent to 3 per cent.

Not only are cancer patients especially vulnerable to the virus, but coming down with it would likely lead to them pausing, permanently stopping or never starting anti-cancer treatment, inevitably leading to a higher cancer mortality rate down the road.

The motivation to protect cancer patients by vaccination is therefore strong.

Concerns over such a vaccination strategy, however, arise from cancer patients being in a potentially immunocompromised state.

Cancer patients have immune systems that are potentially affected by the condition of cancer or by cancer-related treatment.

Hence, they are often considered a "different breed" when it comes to consideration of the balance between risks and benefits associated with vaccination.

A well-functioning immune system is a *sine qua non* (a Latin term for something essential) for vaccination success.

The immune cells, in response to stimulation by a vaccine, must respond appropriately by producing the necessary antibodies to neutralise the offending viruses that enter the body.

Cancer, being a rapidly growing group of cells, imposes a huge drain on the nutrients and energy reserves of the body. Normal cells – immune cells included – are therefore relatively deprived of nutrition and often fail to thrive.

Cancers that arise from the malignant transformation of white blood cells – these being the immune cells of the system – deal a particularly heavy bodily blow to normal immune response as the immune cells themselves have gone rogue. Leukaemia and lymphoma are such cancers.

Many cancer-related therapies, such as radiotherapy and conventional cytotoxic chemotherapy, while suppressing the growth of cancer cells, inadvertently inhibit the normal multiplication of white blood cells and put the immune system on the back foot.

Cancer patients are therefore counting on doctors and scientists to help them answer three critical questions unique to them on receiving Covid-19 vaccination: Does it work? Is it safe? Are all cancer patients the same?

In trying to definitively answer the question of whether cancer patients, both on and off treatment, benefit from Covid-19 vaccination, doctors struggle with the problem of paucity of scientific data as these patients did not, by and large, participate in the clinical trials leading to the approval of these vaccines.

Indirect evidence, however, can be gleaned from the decades of experience with flu (influenza) vaccination in cancer patients.

Cancer patients do mount an immune response and produce protective antibodies (a process known as seroconversion) in response to flu vaccination.

Ample clinical evidence indicates that the mortality from influenza among cancer patients can be decreased substantially with the help of the flu vaccine.

Since direct clinical trial experience of Covid-19 vaccination in cancer patients does not look to be rapidly forthcoming, and given the elevated threat that such patients face from the virus, it is not beyond the pale to extrapolate from the flu vaccination data and conclude that vaccination is likely to confer protection on them.

Chemotherapy, in causing a less-than-perfect immune response, will probably lead to some degree of attenuation in the seroconversion and, hence, the protection rate.

Cancer immunotherapy and hormonal therapy (also known as endocrine therapy) will likely not have such an issue.

Conceivably, severely immunosuppressive treatments such as stem cell transplant (bone marrow transplant) or treatment directed against antibody-producing immune cells (known as B-cells) will have the most profound impact and substantially water down the vaccine protection rate.

With the exception of patients receiving such treatments, other cancer patients should probably mount a fairly efficient immune response to vaccination.

Given a choice, is there an optimal timing that cancer patients should pick to undergo vaccination? It is probably best to get it done before the commencement of anti-cancer treatment, while the immune system is fairly robust.

The next question is: Is it safe?

Currently developed Covid-19 vaccines are, thankfully, from the point of view of cancer patients, not live vaccines.

In general, the use of live vaccines in cancer patients with an impaired immune system is ill advised.

Pretty severe infective complications have occurred in the past with the use of BCG (Bacillus Calmette-Guerin) vaccines against tuberculosis in this vulnerable group. Current Covid-19 vaccines in use in the world are either mRNA-based or non-replicating vaccines which are unable to make new viral particles.

Cancer doctors have been experimenting with anti-cancer vaccines that are mRNA-based for more than a decade.

While therapeutic success against cancers has yet to be achieved, oncologists at least have gathered from such experiments that mRNA-based vaccines can be safely administered to cancer patients.

Is there a particular vaccine that will suit cancer patients better? From a safety perspective, no. Both mRNA-based and non-replicating vaccines using inactivated viral particles or vectors should be fairly safe.

Finally, we come to the question of whether all cancer patients should be treated the same way, or if they should be stratified.

Broadly, we can group cancer patients into an active group still on treatment, a chronic group in remission on a treatment holiday and a survivorship group potentially cured of their cancers.

Singapore has adopted an approach of vaccinating the chronic group (with the proviso that they are off treatment for at least three months, with no plans to start further treatment in another two months) and the survivorship group (who are either not on treatment or on only hormonal treatment).

The active group is currently excluded from Singapore's vaccination programme.

This decision is likely made with abundant caution, out of concern over the ability of these patients to mount an immune response to the vaccine and safety issues.

International trends are moving towards vaccination of most, if not all, cancer patients.

The European Society for Medical Oncology has made a call to action to vaccinate all cancer patients.

The American Cancer Society wrote an open letter to appeal to the governors of all states in the United States to prioritise the vaccination of cancer patients.

Once our local medical community has gained a sufficient level of comfort over the likelihood of the benefits substantially outweighing the risks of vaccination, Singapore should move quickly towards not only including but also prioritising all cancer patients in our vaccination programme.

The motivation to protect cancer patients with Covid-19 vaccination is strong. Not only are they especially vulnerable to the coronavirus, but coming down with it would likely lead to them pausing, permanently stopping or never starting anti-cancer treatment, inevitably leading to a higher cancer mortality rate. But concerns arise from their potentially immunocompromised state. ST PHOTO: CHONG JUN LIANG

About the writer

Dr Wong Seng Weng is medical director and consultant medical oncologist at The Cancer Centre of the Singapore Medical Group. His subspecialities include breast cancer, lung cancer and gastrointestinal cancers.