"Novel way of administering an oral anti-angiogenic agent to normalize tumour blood vessels and improve tumour blood flow so as to enhance chemotherapy efficacy in breast cancers"

FACTSHEET

Chemotherapy in breast cancer

Chemotherapy is usually given after breast cancer surgery to prevent cancer recurrence in early stage disease. It may also be given before surgery to shrink large tumours before they are surgically removed. Chemotherapy is usually given over a period of 3 to 6 months. The choice of drugs depends on the patient's general health and other medical problems, stage of cancer, and other risk factors.

How anti-angiogenic agents may complement chemotherapy

Like other tumours, breast cancers have their own blood supply. Many have abnormal blood vessels that are grown in a process called angiogenesis as the tumours secrete vascular endothelial growth factor (VEGF). These blood vessels tend to be unevenly distributed and chaotic compared to normal blood vessels that are evenly spaced and well differentiated. Tumour blood vessels are also often leaky, making it difficult for chemotherapy drugs to be delivered into the tumour.

Sunitinib is an oral anti-angiogenic agent that prevents abnormal blood vessels in tumours from growing by targeting the receptor that VEGF binds to. Its mechanism of action is slightly different from that of Avastin (bevacizumab), a drug administered intravenously, which neutralizes VEGF, and which is approved for use in colorectal, kidney and lung cancer.

Sunitinib is currently approved by the United States Food and Drug Administration for the treatment of kidney cancer as a standalone drug not in combination with chemotherapy. It is usually given in 3 capsules totalling 37.5mg daily for a continuous period of time. Prolonged use is associated with potentially severe side-effects such as hypertension, diarrhoea, and low blood counts.

The discovery: low-dose sunitinib improves tumour blood flow and chemotherapy efficacy

Combining an anti-angiogenic agent with chemotherapy has been a strategy that has been actively evaluated in recent years to improve cancer treatment efficacy. However, all previous studies that have attempted to combine an oral anti-angiogenic agent that targets the receptor that VEGF binds to (*e.g.*, sunitinib) in combination with standard chemotherapy in common solid tumours (*e.g.*, breast cancer, colorectal cancer) have failed to improve treatment outcome over standard chemotherapy alone.

The research team hypothesized that these earlier studies failed because full strength continuous dosing of the oral anti-angiogenic agent was administered together with chemotherapy in these studies, which over time, will result in destruction of tumour blood vessels. When used in combination, this strategy becomes counter-productive as chemotherapy cannot be delivered into the tumour. The research team further hypothesized that a lower dose of an oral anti-angiogenic agent given intermittently for a short period of time before chemotherapy would be more effective than a prolonged, continuous dose. This

National University Health System Pte Ltd, 1E Kent Ridge Road, Singapore 119228
Tel: (65) 6779 5555, Fax: (65) 6779 5678, www.nuhs.edu.sg, Company Registration No. 200801778C

is because pre-clinical studies have shown that a lower-dose, shorter-duration of an oral anti-angiogenic agent normalizes blood vessels, while higher doses and/or more prolonged treatment will ultimately destroy tumour blood vessels. The normalization window was identified to be between 2 to 7 days as determined by previous pre-clinical studies.

This randomized clinical study was conducted in two phases and involved 21 breast cancer patients at the National University Hospital, Singapore. The oral anti-angiogenic agent that was studied was sunitinib.

Phase 1 consisted of identifying the ideal dose of sunitinib that would curb the growth of abnormal blood vessels and promote the growth of normal blood vessels within the tumour. Patients received 12.5 or 25mg of sunitinib for one week prior to chemotherapy. At 25mg, anti-angiogenic effect (reduced tumour blood flow) was observed, suggesting that even the lowered dose of 25mg was too high. Patients who received 12.5mg of sunitinib, however, experienced an increase in tumour blood flow suggesting that the dose was sufficient to allow the normalisation of blood vessels in the tumour. Microscopic examination of the tumour after treatment also showed normalization of blood vessels. The Phase 2 trial dose was thus set at 12.5mg.

In Phase 2, patients were randomised to receive standard chemotherapy (doxorubicin/cyclophosphamide) with or without pre-treatment with 12.5mg of sunitinib for 1 week. After 1 cycle, tumour size was measured using magnetic resonance imaging (MRI). The results showed a greater reduction in tumour size for patients pre-treated with sunitinib. Biopsies were also performed after 1 cycle of chemotherapy to assess the tumour response examined under the microscope. More tumours that were pre-treated with sunitinib had grade 4 response on a scale of 1-4, with 4 being the best response, than patients who received standard chemotherapy alone. Patients treated with sunitinib and chemotherapy who went for surgery were also more likely to have negative lymph nodes compared to those on chemotherapy alone. These preliminary results suggest that pre-treating cancer patients with low-dose, short-course sunitinib before standard chemotherapy may improve the treatment response by normalizing blood vessels and improving drug delivery.

Researchers involved in the trial
Dr Lee Soo Chin, Associate Director (Research) and Senior Consultant, Department of Haematology-Oncology, National University Cancer Institute, Singapore was the principal investigator of the trial. Researchers from the National University Cancer Institute, Singapore, Haematology-Oncology Research Group, Cancer Science Institute, National University of Singapore, National Cancer Centre Singapore, and Clinical Imaging Research Centre, Singapore were also involved.

Significance of findings
By using FDA-approved sunitinib in a novel way, the research team was able to normalise tumour vasculature to enhance the efficacy of chemotherapy.

These findings suggest that a low dose of 12.5mg sunitinib for one week may potentially improve chemotherapy drug delivery and treatment outcome.

Moving forward, the team will conduct further studies. These may include a Phase 3 randomised trial, where the combination may be given randomly to larger numbers of patients to confirm its effectiveness, monitor side effects, compare it to commonly used

National University Health System Pte Ltd, 1E Kent Ridge Road, Singapore 119228
Tel: (65) 6779 5555, Fax: (65) 6779 5678, www.nuhs.edu.sg, Company Registration No. 200801778C

treatments, and collect information that will allow the drug or treatment to be used safely. The team may also explore the combination of sunitinib with other types of chemotherapy drugs that may be more optimally combined with sunitinib without significant added side effects.

National University Health System Pte Ltd, 1E Kent Ridge Road, Singapore 119228
Tel: (65) 6779 5555, Fax: (65) 6779 5678, www.nuhs.edu.sg, Company Registration No. 200801778C