PHILIPS

Backgrounder

Ultrasound-mediated MRI-guided drug release from temperature-sensitive liposomes

Cancer chemotherapy treatment

A number of options are available for the treatment of cancer, ranging from invasive surgery to non-invasive radiotherapy, thermal ablation, chemotherapy and others. In all cases, the goal is to eliminate all cancerous tissue in the body while minimizing harm to healthy tissue. The specific treatment or combination of treatments depends on the nature and the stage of the cancer.

Chemotherapy constitutes part of the therapy regime for around 50% of cancer patients. Once administered, the chemotherapy drugs circulate freely in the blood stream and attack rapidly dividing cells. In this way, they are effective against cancer cells. However, they also attack normal healthy cells that rapidly divide, such as those in bone marrow, the digestive tract and the hair follicles. Side effects of chemotherapy include anemia (reduced red blood cell count), neutropenia (reduced white blood cell count), bleeding and an increased risk of opportunistic infections. Keeping these side effects under control often limits the tolerable chemotherapy dose to a level well below that required for optimum eradication of tumors. For some cancers, a more localized delivery of chemotherapy treatment may allow an increase in the deliverable dose to the tumor and improve the effectiveness of the treatment.

Chemotherapy treatment is complicated by the fact that tumors are not homogenous structures in relation to their blood supply. Some parts of a tumor may therefore be well perfused with blood, while others may be poorly perfused. The inner part of a tumor, for example, being remote from local vasculature, is often poorly perfused (this often results in it having a so-called necrotic core). As a result, chemotherapy drugs are not taken up evenly, with poorly perfused regions receiving sub-optimal doses. This is believed to be one of the reasons why tumors sometimes re-grow after what at first appears to be successful therapy.

Methods to increase local chemotherapy uptake may therefore improve the effectiveness of the therapy while limiting the adverse effects. In addition, a method of rapidly visualizing and measuring local drug uptake could aid clinicians in deciding whether additional therapies are needed to insure the complete eradication of tumors.

Ultrasound triggered local drug delivery

Focused ultrasound has been proposed as a method of increasing the relative uptake of chemotherapy drugs in tumors compared to healthy tissue. When focused on one point, a pressure pulse or local heating may result, depending on the exact characteristics of the sound waves. This pressure or temperature change can be exploited in ultrasound mediated drug delivery.

Pressure-mediated local drug delivery
One pressure-mediated local drug delivery technique uses blood-borne 'microbubbles' (microscopic hollow spheres). These can be tracked using ultrasound imaging, which allows the technique to be image-guided. When the microbubbles arrive at the target region, they are made to burst (cavitated) using an ultrasound pulse of sufficient energy and at the right frequency, in much the same way that a wine glass can be shattered by an opera singer.

The bursting of the microbubbles increases the porosity of the tissue and adjacent cell walls in the targeted region (a process known as sonoporation), allowing co-injected drugs to be more easily absorbed and hence improving drug uptake. Sonoporation is of special significance in the delivery of therapeutic molecules that are not normally taken up well by cells, with siRNA or pDNA being the most prominent examples.

Temperature-mediated local drug release under MRI guidance
The focus of this backgrounder is a local drug delivery technique being investigated by Philips and TU/e researchers that combines MRI, ultrasound and small drug containing particles. The technique employs chemotherapy drugs that are sealed inside lipid-walled particles called liposomes. Stable at normal body temperature (37℃), the liposomes stop their drug payload from diffusing into the blood and therefore exhibit minimal toxicity. However, at around 42℃ they become leaky, rele asing their payload. Drug release from the liposomes is stimulated by locally heating the target area to 42℃ using a High Intensity Focused Ultrasound (HIFU) beam.

Pre-operative tumor identification and procedure planning, as well as guidance of the ultrasound heating, are carried out using magnetic resonance (MR) imaging. Real-time MRI tissue temperature measurements of the target tumor area enable closed-loop control of the ultrasound heating process. This technique allows homogeneous heating of tumor tissue to a temperature of 42℃ with a precis ion of +/- 0.8 ℃.

In order to monitor the drug release and uptake in the tumor, the lipsosomes are also loaded with a clinically used MRI contrast agent which is co-released upon heating. The release of the contrast agent, monitored with MRI, can be used to measure and visualize drug uptake in the tumor and surrounding tissue.

The Philips and TU/e pre-clinical work was performed using temperature-sensitive liposomes loaded with the anti-cancer drug doxorubicin and a gadolinium-based MRI contrast agent. The experiments were performed on a 3-Tesla MR-HIFU scanner (Sonalleve) modified for the pre-clinical investigations. The preclinical studies showed proof-of-concept of the local drug release technique and the resulting drug uptake, measurement and visualization. Direct measurements of drug uptake in the tumor were found to be increased by a factor of between 2 and 5 (even higher in later, as yet unpublished, studies) depending on the nature of the tumor. Early visualization results indicate that the technique may be capable of identifying regions within a tumor that are poorly perfused with blood. This may provide an indication if the treatment was effective and allow early identification of the need for alternative therapy.

These proof-of-concept studies show the promise of ultrasound-mediated MRI-guided local drug delivery using temperature-sensitive liposomes. The technique may enable increased drug concentration within tumors, maximizing therapeutic effect while limiting adverse effects. It may also provide rapid feedback on the likely effectiveness of the therapy to aid in planning of further treatment steps. Building on the current proof-of-concept results, further pre-clinical studies are being performed to assess the therapeutic value of the technique. This is the next necessary step in the process of pre-clinical and then clinical investigations, leading to potential future patient applications.