Preventing chemotherapy from overstaying its welcome

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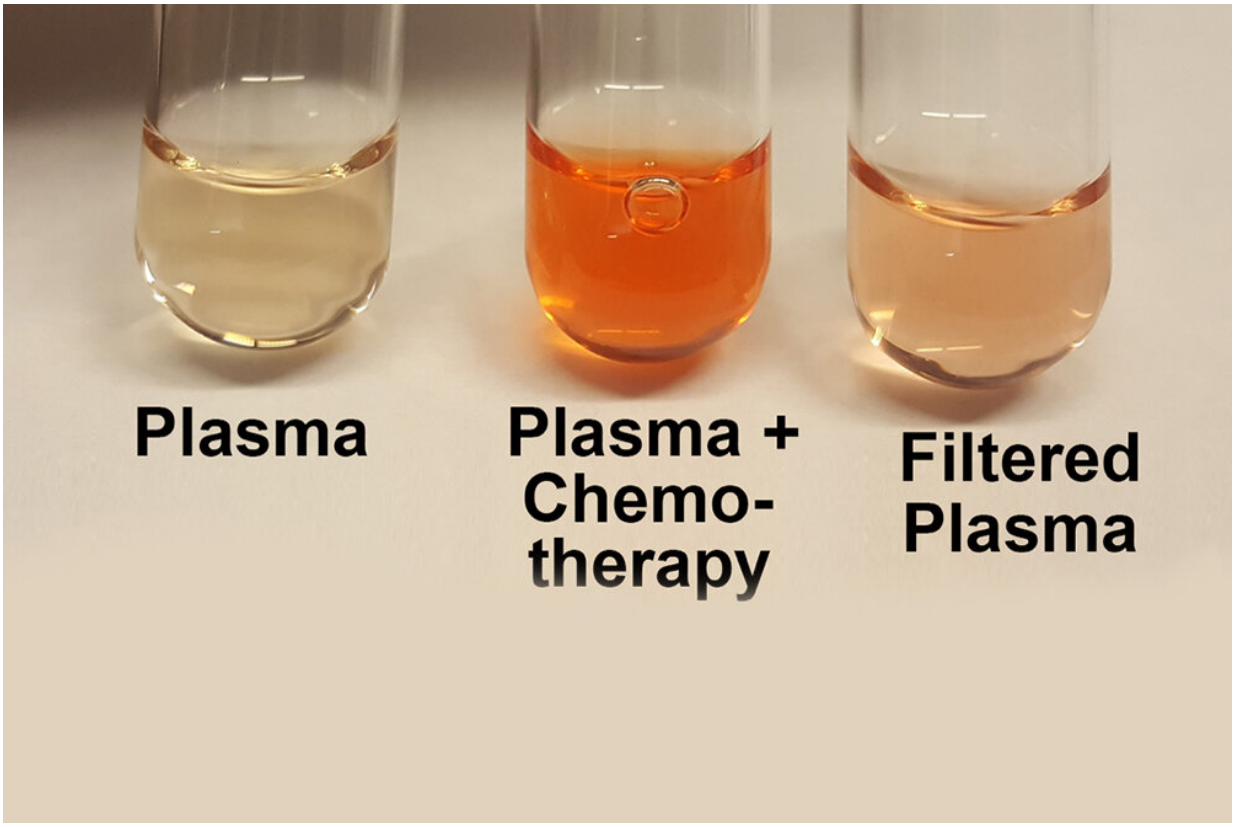

Test tubes with plasma, plasma plus chemotherapy and filtered plasma. Credit: Originally published in Cancers

For patients with cancer, the tumor-killing power of chemotherapeutic drugs is a double-edged sword. While many cancer drugs kill tumor

cells, they can also harm healthy cells as they travel throughout the bloodstream.

"A major limitation of chemotherapy agents is that only a tiny fraction goes to their targeted tumor," said Dieter Haemmerich, Ph.D., D.Sc., professor at the Darby Children's Research Institute within the Department of Pediatrics at the Medical University of South Carolina (MUSC). "As a result, there are side effects that include damage to the heart."

But what if you could "cleanse" the blood of chemotherapeutic drugs to reduce their harmful side effects?

In an article published in March 2022 in the journal *Cancers*, an MUSC research team led by Haemmerich reported that it had developed a device to remove excess chemotherapeutic drugs from circulation after cancer treatment. Using this device, the team removed 30% of the administered drug by one hour after treatment. Seed funding to develop the device was provided by a High Innovation—High Reward grant from the South Carolina Clinical & Translational Research Institute's pilot project program.

Haemmerich and his colleagues, including Katherine Twombley, M.D., a professor in the MUSC Department of Pediatrics, Division of Pediatric Nephrology, focused on doxorubicin (DOX), which is one of the most widely used chemotherapy drugs in adults and children.

DOX is also known to be toxic to the heart. This toxicity is particularly detrimental in pediatric patients, since any resulting heart failure will have negative health effects for the rest of the child's life. In a 2006 clinical trial, DOX reduced cardiac function in children with leukemia, and steroid therapy was required to reduce its damaging effects.

Despite its toxicity to the heart, DOX is a popular chemotherapy drug because it is highly effective at stopping cancer cells from dividing.

"Doxorubicin works by basically damaging DNA," said Yuri Peterson, Ph.D., an associate professor in the Department of Drug Discovery and Biomedical Sciences in the MUSC College of Pharmacy and an author of the article. "That is useful for treating cancer, but it can also cause off-target side effects like hair and bone marrow loss."

Recent efforts to target DOX more precisely to the tumor site have included encapsulating it inside temperature-sensitive nanoparticles. These tiny particles are intact at normal body temperature and carry the drug through the bloodstream to the tumor. There, they can be heated with a probe to around 105 degrees Fahrenheit to release their DOX cargo.

However, the technique has its own limitations. Only a fraction of the administered nanoparticles release their cargo when the heat is applied at the tumor site. Once the nanoparticles break down in the body, which can take as little as an hour, the remaining drug enters the bloodstream and can then cause side effects.

The MUSC research team wanted to improve outcomes with this technique by developing a device that would remove the leftover DOX after treatment.

Using a rodent model of cancer, the researchers injected the heat-sensitive DOX nanoparticles and applied heat at the tumor site to release DOX. After treatment, they cleansed the blood of leftover DOX by first passing it through a heating element to get the nanoparticles to release the drug and then through an activated carbon filter to remove the drug from the blood before it was returned to the rodents' circulation.

Marissa Wolfe, D.V.M., associate professor in the Department of Comparative Medicine at MUSC, was instrumental in developing surgical methods to implant catheters in the rodents' small vessels to enable blood to pass through the filtration device.

Krishna Ramajayam, Ph.D., a postdoctoral fellow in Haemmerich's laboratory in the Division of Pediatric Cardiology at MUSC, designed the heating element in the filtration device and supported the imaging studies for monitoring drug release and filtration.

"Since the device is computer controlled, you can have very precise heating to ensure that the drug is released," said Ramajayam. "The most exciting part for me is addressing both delivery and removal of the drug, which will improve patients' quality of life immensely."

Importantly, the team also developed a method for detecting drug levels in the blood in real time to ensure that the drug is effectively removed.

"By imaging the blood before and after filtration, we can actually predict how much drug is being removed in real time in the clinic," said Anjan Motamarry, Ph.D., who completed work on the study while a doctoral student in Haemmerich's lab before transitioning to a job in industry. "This would be very useful information for a clinician who needed to make a decision about when to stop filtration."

Reducing the exposure of patients to leftover chemotherapy drugs could allow them to recover faster, with fewer side effects. It could also enable them to receive more chemotherapy cycles in the future in case additional treatment is necessary to kill the cancer cells.

"Every drug has a maximum tolerated dose that you cannot go beyond," said Motamarry. "Since we are removing the leftover drug after treatment, you can actually give an additional dose if the first cycle is not

sufficient, which would not be possible if the drug was not removed."

Filtering the blood through the device also led to nearly three times less DOX in the heart, as measured using mass spectrometry at the MUSC Drug Discovery Core. Peterson and Thomas Benton, Ph.D., who was a doctoral student at MUSC at the time of the study, performed the measurements.

These promising results suggest that the new device could reduce side effects in the heart that can be caused by chemotherapy, but more studies will be needed to confirm that promise.

"If you deliver less drug to the heart, you will probably have fewer side effects," said Haemmerich. "Our next step is to test the function of the heart directly after using this method in long-term animal tumor studies."

Further improvements to their device may one day improve the effectiveness and safety of chemotherapy in children and adults.

"It's really hard for anyone to go through chemotherapy," said Motamarry. "This is the least that we can do to make it easier for them."

More information: Anjan Motamarry et al, Extracorporeal Removal of Thermosensitive Liposomal Doxorubicin from Systemic Circulation after Tumor Delivery to Reduce Toxicities, *Cancers* (2022). DOI: 10.3390/cancers14051322

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