Researchers of the Leiden University Medical Centre (LUMC) and the Leiden Institute of Chemistry have made an important discovery about the commonly used anti-cancer drug doxorubicin. They have found a way to reduce its side effects without sacrificing the effectiveness of the medication. This is encouraging because the serious side effects are often a reason to discontinue treatment.

Their discovery runs very much counter to the existing dogma that it has taken years to get the article published. Ph.D. candidate Sabina van der Zanden explains that it can now be read in the scientific journal *PNAS*. “Doxorubicin had already been used for chemotherapy for decades. It had always been thought to kill cancer cells by causing breaks in their DNA, but we’ve discovered that things are more complicated than that. It took quite a while before colleagues would believe us.”

**Combination causes side effects**

The researchers had already discovered that doxorubicin works in two different ways. It does indeed make breaks in the DNA, but it also causes damage to chromatin, a kind of marbles inside the cell nucleus around which the DNA is wrapped. Each of these actions can lead to the death of the cancer cell. It now turns out that the combination of these actions is the cause of the serious side effects, such as heart failure, infertility, and secondary tumors. These side effects are often a reason to cease the chemotherapy sooner or to not even start it at all.

**Variant without DNA fractures**

By studying the structure of the molecule, the researchers determined which part was responsible for the DNA breaks. Armed with that knowledge, and in collaboration with colleague Dennis Wander led by Hermen Overkleeft (Leiden Institute of Chemistry), they produced a variant of doxorubicin that did not cause DNA breaks but that did damage the chromatin. "The exiting biology has taught us chemists a lot and moreover the chemical structures make the anthracycline class of biomolecules a great target to work on as organic chemist—we will likely continue for quite a bit making these wonderful compounds," says Dennis Wander.

Experiments with laboratory animals and human cells showed that this variant does not cause heart failure but still kills tumor cells. "It was very encouraging to see that what we had come up with by means of chemistry actually works in living cells," says Van der Zanden.

**Serious side effects are history**
With this discovery, the researchers have thus uncoupled the anti-cancer effect of doxorubicin from its serious side effects. The next step is to test more new variants to further fine-tune which part of the molecule has what effect and under what conditions. The researchers will also continue studies on laboratory animals and ultimately patients, with the eventual aim being to make longer treatment possible.


Provided by Leiden University


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