Potential for Improving Cancer Treatment by Optimising Drug Scheduling

Professor Nicola Curtin

JUNE 2025

doi.org/10.33548/SCIENTIA1285

MEDICAL & HEALTH SCIENCES

Scientia

Potential for Improving Cancer Treatment by Optimising Drug Scheduling

Cancers often develop because of faulty DNA repair systems. PARP inhibitors (PARPi) are a class of targeted anti-cancer drugs that exploit this weakness, by inhibiting a complementary DNA repair system, to selectively target the tumour. However, these medicines need to be taken every day, creating a burden on patients and reducing the options for combination with other anticancer therapies. Professor Nicola Curtin and her team at Newcastle University investigated how long different PARPi stay active in cancer cells after a single dose and how this influences their effectiveness when combined with another anti-cancer drug.

The Urgent Need for Better Cancer Treatments

In the UK, it is widely quoted that 1 in 2 people will be diagnosed with cancer, and that every four minutes, someone dies from cancer. These sobering statistics reflect the urgent need for better cancer treatments, and scientists around the world are working to find and test new drugs. Among them is Professor Nicola Curtin, at Newcastle University in the UK, who led a team of researchers dedicated to understanding cancer biology, and how this knowledge can be used to create more effective therapies.

Our cells are constantly at work – growing, dividing, and renewing themselves to keep our bodies healthy and functioning. To divide they need to replicate their DNA, but DNA is constantly being damaged by normal "wear and tear". If this damage is not repaired, because of faulty DNA repair systems, mistakes, called mutations, occur. Accumulation of mutations can result in the development of cancer.

PARP Inhibitors (PARPi) Target DNA repair

PARPi are a type of targeted cancer therapy that work by blocking a protein called PARP, which helps repair damaged DNA in cells. Healthy normal cells, can tolerate PARPi because they have alternative DNA repair systems, but some cancer cells already have faulty alternative DNA repair systems. When a PARP inhibitor is used in these cancer cells, it creates a 'synthetic lethality' effect: both of the cell's main repair systems are disabled, so the cancer cell can't fix its DNA and dies (see figure). Because PARPi specifically target this weakness in cancer cells, they can be more effective and more gentle than traditional treatments, such as chemotherapy.

PARPi medicines have been approved by regulatory bodies such as the FDA and European Medicines Agency for about a decade for use against types of ovarian, breast, prostate, and pancreatic cancers. There are multiple different PARPi drugs with slightly different properties but all are given to patients once or twice a day. For them to be effective, PARP must be completely and continuously inhibited.

ATR inhibitors are another type of anti-cancer drug that work by preventing cancer cells from repairing DNA damage. Previous laboratory research has shown that PARPi and ATR inhibitors work even better together, and now researchers are testing this powerful combination in clinical trials with patients.

Testing How Long PARP Inhibitors Last

Professor Curtin and her team conducted experiments to understand how long after treatment with PARPi drugs their effects remain, and how PARPi drug timings affect efficacy when combined with an ATR inhibitor.

The team tested five different PARPi medications: rucaparib, olaparib, niraparib, talazoparib, and pamiparib, against two different types of ovarian cancer cell. They also investigated how the timing of doses impacts ATR inhibitor and PARPi combination therapy. To mimic brief drug exposure, the cancer cells were treated with each drug for one hour and then washed. A standard laboratory test was then used to check how active PARP was within the cells during this treatment and immediately after the wash (0 hours), as well as at 1, 24, 48, and 72 hours afterwards.

To see how timing impacts combination therapy, the cancer cells were exposed to both types of treatments at different timings, and the number of surviving cancer cells was measured after

10 days. Cells were exposed to both PARPi and an ATR inhibitor at the same time for 24 hours, or PARPi for 24 hours and then the ATR inhibitor for 24 hours, or PARPi for 24 hours, followed by a 24-hour drug-free break, and then the ATR inhibitor for 24 hours. These carefully designed experiments allowed the team to explore not just how effective each individual drug was, but how timing and sequencing impacted their usefulness.

Rucaparib's Lasting Impact on Cancer Cells

The results showed striking differences in how long each drug remained effective. Rucaparib stood out for its durability – PARP activity in the cancer cells remained strongly suppressed (over 75% inhibited) even three days after the drug was removed. In contrast, olaparib and niraparib lost their effects much more quickly, with little to no inhibition left at the 72-hour mark. Talazoparib and pamiparib showed intermediate levels of activity, fading over time but not as quickly as olaparib and niraparib.

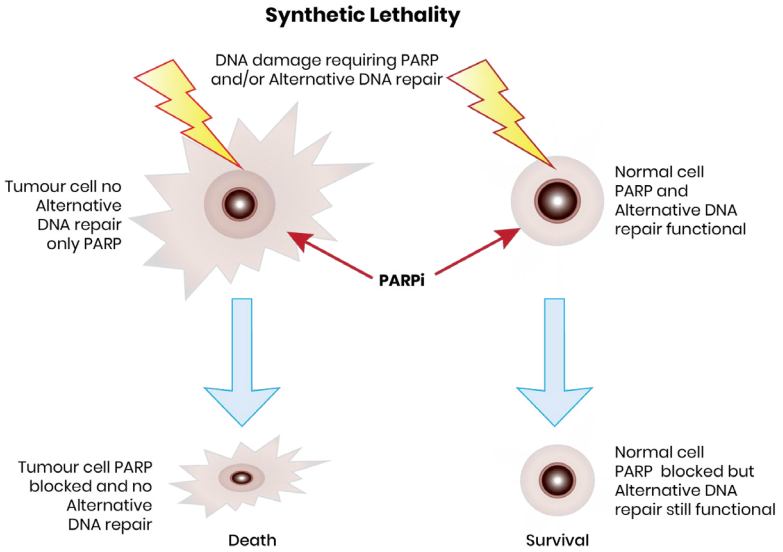
When the PARPi medicines were combined with an ATR inhibitor, rucaparib again performed best. It enhanced the cancer-killing effect of the ATR inhibitor across all schedules, whether the two drugs were given at the same time, one after the other, or even with a 24-hour gap in between. In contrast, olaparib and niraparib only boosted the ATR inhibitor's effects when given at the same time. They lost effectiveness when used sequentially or with a delay, likely because they no longer remained active in the cells.

Why This Matters for Patients

Professor Curtin and the team's findings have meaningful implications for how we treat cancer. Right now, PARPi medicines are usually taken once or twice every day, for long periods. This is based on the understanding that they need to be in the body constantly to work. However, this study suggests that this might not be necessary for every drug. Rucaparib's long-lasting effects mean it could potentially be given less frequently without losing its ability to block cancer cell repair. For patients, that could translate to fewer side effects, more convenient treatment schedules, and better quality of life during therapy. Importantly, this approach might also help reduce treatment costs, making these targeted therapies more accessible, particularly for people in low- and middle-income countries where affordability can be a major barrier to cancer treatment.

The study also highlights how crucial timing and drug selection are when using combination treatments. If a PARPi medicine like olaparib or niraparib loses its effect quickly after it's removed, it may need to be taken at the exact same time as an ATR inhibitor to work. However, a more durable drug like rucaparib offers greater flexibility, making it easier to design effective combination therapies that may also have reduced side-effects.

Recently, a clinical trial in India enrolled nine patients with platinum-sensitive (a surrogate for the alternative DNA repair pathway defect) ovarian cancer. They were treated with rucaparib (600 mg twice per day) every 3–4 days instead of every day. PARP activity in their blood was also measured 72 hours after the dose. Those with large tumours still progressed – but three patients who still had durable PARP inhibition at 72 hours also had durable responses for 62, 68, and 88 weeks. A further three patients, who had been receiving PARPi therapy but experiencing toxicity, opted for the same schedule of rucaparib. They also responded well, without toxicity, for 62, 96, and 132 weeks. It was concluded that the intermittent regime was tolerable for more than 12 months, without toxicity and improved quality of life, and that the regimen is effective in patients with durable PARP inhibition.



> When a PARPi is used in cancer cells with faulty DNA repair systems, it creates a 'synthetic lethality' effect: both of the cell's main repair systems are disabled, so the cancer cell can't fix its DNA and dies.

Now, a Phase 2 randomised clinical trial is being funded by the Indian Council of Medical Research to compare intermittent bi-weekly rucaparib (1200 mg twice a week) to the standard of care daily regimen (1200 mg per day).

This work represents an exciting development in cancer treatment. It will allow for more research and clinical trials to understand how to schedule PARPi medicine dosing most effectively, and whether rucaparib could be a good partner for other DNA damage targeting drugs. Professor Curtin and her team's work investigating the unique behaviour of each PARPi medicine is a crucial step towards more personalised, effective, and patient-friendly cancer care.

Article written by Helen Rickard, PhD

MEET THE RESEARCHER

Professor Nicola Curtin
Faculty of Medical Sciences, Newcastle University, Newcastle, UK

Nicola Curtin is Professor Emerita at Newcastle University, where she began her postdoctoral career in 1982. Professor Curtin is a world-renowned cancer researcher, focusing on the DNA damage response, including the development of drugs that target this response, and the identification of predictive biomarkers. Her greatest contribution is the development of the PARP inhibitor (PARPi), rucaparib (Rubraca®) and the identification of the synthetic lethality of PARPi in tumours with specific DNA repair deficiencies, recognised as a paradigm-shifting milestone in cancer research https://www.nature.com/immersive/d42859-020-00083-8/index.html. She is a fellow of the Academy of Medical Sciences. She was awarded the Robert R. Ruffolo Career Achievement Award in Pharmacology by the American Society for Pharmacology and Experimental Therapeutics in 2021. In 2022, she was awarded the Heatley Medal and Prize by the Biochemistry Society, and in 2023, the Genome Stability Network Medal for her outstanding contribution to the field, as well as winning the Lifetime Achievement Award by Educate North, and was the University of Surrey Alumna of the year. Alongside her academic research, Professor Curtin serves as the Editor-in-Chief for the journal *Expert Reviews in Molecular Medicine* and has held positions on the advisory boards of several cancer charities and research foundations, as well as consultancies with pharmaceutical companies. In recognition of the significant impact of her work, Professor Curtin is a highly ranked researcher both in terms of lifetime publications and those over the past five years at Scholar GPS.

CONTACT

nicola.curtin@newcastle.ac.uk
https://scholargps.com/scholars/49002345656044/nicola-j-curtin
https://www.ncl.ac.uk/medical-sciences/people/profile/nicolacurtin.html

FUNDING

This research was funded by Seed-corn funding from CRUK - Department of Biotechnology India - Wellcome Trust India Alliance Affordable Approaches to Cancer

This article was partially funded by an unrestricted educational grant from pharma&

Professor Curtin has provided speaker/consultancy services to pharma&, with fees donated to the Community Foundation charity

FURTHER READING

H Smith, E Willmore, A Mukhopadhyay, *et al.*, Differences in Durability of PARP Inhibition by Clinically Approved PARP Inhibitors: Implications for Combinations and Scheduling, *Cancers*, 2022, 14(22), 5559. DOI: https://doi.org/10.3390/cancers14225559

Newcastle University