ILLUSTRATION BY ANTOINE DORE

After the breakthrough

The introduction of PARP inhibitors changed how ovarian cancer is treated and managed, but there is still more to come from these drugs. **By Simon Makin**

Ovarian cancer has a poor prognosis, mainly because it is usually at an advanced stage by the time it is detected. Today 90% of people with breast cancer will be cured, whereas 50% of those with ovarian cancer will die within five years of diagnosis. The standard care for ovarian cancer — a combination of surgery and chemotherapy — has remained almost unchanged since the 1960s. But over the past several years, a new class of drug has begun to transform the treatment of ovarian cancer.

Called poly(ADP-ribose) polymerase inhibitors — PARP inhibitors for short — the drugs work by blocking enzymes involved in DNA repair processes that cancer cells rely on as they multiply. "PARP inhibitors are the breakthrough story for ovarian cancer over the past decade," says oncologist Daniela Matei at Northwestern University in Chicago, Illinois.

Clinical trial findings over the past three years have resulted in PARP inhibitors being used to treat people who have been newly diagnosed, rather than being used only after other therapies have failed. Two such inhibitors have been approved for first-line maintenance use so far, with others waiting hopefully in the wings (maintenance treatments are those given after chemotherapy with the aim of preventing or delaying recurrence). As their numbers grow, so too might their applications. PARP inhibitors were developed to fight cancers with *BRCA* mutations, which greatly increase a person's risk of developing breast and ovarian cancer, but mounting evidence points to benefits in people without these mutations, too. Researchers are looking to build on these successes by developing better PARP inhibitors, searching for synergies with other drugs, and improving predictions of who will benefit.

Doubling up on DNA

PARP inhibitors exploit a principle known as synthetic lethality, in which two defects become fatal to a cell when combined. The drugs target PARP enzymes, which are responsible for initiating an important mechanism of repairing breaks in single strands of DNA. The inhibitors block this process, causing single-strand breaks to progress into double-strand breaks.

In most cells, another mechanism for fixing double-strand breaks, known as homologous recombination, can then step in and save the cell. However, in some cells this second line of defence is also impaired — a condition called homologous recombination deficiency (HRD). Around half of ovarian cancers exhibit HRD, and roughly one-fifth of those are due to mutations in the *BRCA* genes, which code for proteins involved in DNA repair[1]. Put simply, *BRCA*-mutant cells lack the ability to repair the damage done by PARP inhibitors.

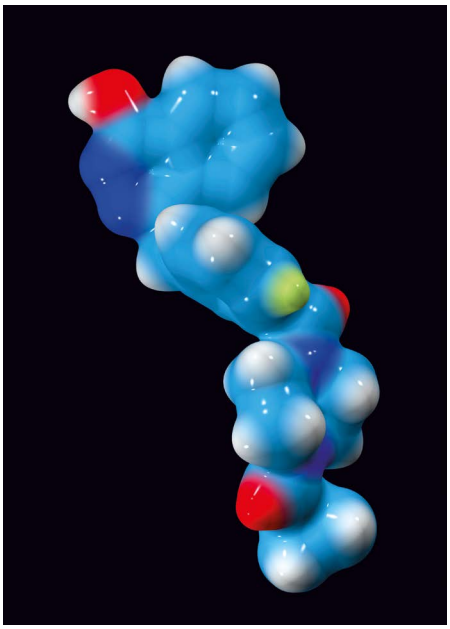
Two studies, published simultaneously in *Nature* in 2005, showed that human cancer cells with *BRCA* mutations are supremely vulnerable to PARP inhibitors[2,3]. Clinical trials followed, and the first PARP inhibitor — olaparib — was approved in 2014. Rucaparib and niraparib followed soon after, all three were approved to treat advanced, recurrent cancers with *BRCA* mutations.

The efficacy of these drugs is now well-established, improving the length of time people remain alive without their tumours growing (called progression-free survival) by around six months. The use of these drugs was eventually extended to a maintenance treatment of relapsed disease regardless of *BRCA* status. To qualify for PARP inhibitors as maintenance, however, patients had to have responded to their last chemotherapy. The platinum-based chemotherapy used against ovarian cancer also attacks DNA, so response to that treatment is a good predictor of benefit from PARP inhibitors.

Moving on up

The first people to be given these new treatments are those with advanced, recurrent disease, who might have exhausted other treatment options. Ultimately, researchers, drug companies and patients want to know how a drug performs as part of a first-line treatment package in people newly diagnosed with cancer. "The magnitude of benefit in the upfront setting may be higher, just because the tumour burden is less, the cells are more sensitive," says Matei. The potential benefit could even reach the level of a cure. "There's no possibility of curing patients who have relapsed. As a first-line treatment, there is," says Isabelle Ray-Coquard, an oncologist at the Claude Bernard University in Lyon, France. Accordingly, as soon as the benefits of PARP inhibitors in recurrent disease became clear, a wave of trials testing PARP inhibitors in the first-line setting were initiated.

In the closing days of 2018, a landmark clinical



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The drug olaparib was first approved in 2014.

trial called SOLO-1, which was testing olaparib as first-line maintenance therapy in people with *BRCA* mutations, published remarkable results. The drug improved progression-free survival by around 3 years relative to the placebo — a 260% increase[4]. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) quickly approved olaparib for first-line maintenance use. A follow-up analysis in 2020 showed that the tumours of nearly half of people who had received two years of olaparib as maintenance therapy had still not progressed after five years, compared with only 20% in the placebo group[5]. "Many people in the field, me included, have ventured to say that perhaps a proportion of these patients with *BRCA*-mutated tumours might even be cured," says Matei. "That's something nobody thought was going to be possible in our lifetimes."

Next, researchers wanted to know whether PARP inhibitors could be beneficial in first-line treatment for people without *BRCA* mutations — either those with HRD brought about by other means, or people whose tumours are capable of homologous recombination. In December 2019, the results from three trials of PARP inhibitors used to treat people with newly diagnosed cancer were published. A PARP inhibitor was administered either alone or in combination with other therapies, to people both with and without *BRCA* mutations. The first of these trials, PAOLA-1, combined olaparib with the other drug approved for first-line maintenance treatment at the time: bevacizumab, an anti-angiogenesis agent that starves tumours of oxygen-providing vasculature[6]. The PRIMA trial tested niraparib in people at high risk of recurrent disease[7]. And the VELIA trial tested a fourth drug, veliparib, combined with chemotherapy[8]. Veliparib has slightly different side effects from other PARP inhibitors, including less suppression of blood cells. This means that, unlike the others, it can be given alongside chemotherapy, which itself has a myelosuppressive effect. However, veliparib is not thought to lock PARP enzymes onto damaged DNA as strongly as other inhibitors. Known as PARP trapping, this is crucial to preventing DNA repair. Veliparib might therefore be expected to perform less well as a monotherapy.

Other side effects vary between PARP inhibitors, including fatigue, nausea and hypertension. However, the 5-year follow-up of SOLO-2 (which tested olaparib in recurrent disease) found an 8% incidence of blood cancers in people receiving olaparib compared with 4% in the placebo group (see go.nature.com/3d61apn). "It's a major concern," says Matei. Researchers currently cannot predict who will develop this, and don't know if treatment duration is a factor, she adds. Because chemotherapy can also have these effects, it is not completely clear what is causing what, but physicians will be carefully monitoring patients.

These trials differed in many ways, so comparisons between them are problematic. Nevertheless, all three showed a significant improvement in progression-free survival, in all treated participants, compared with a placebo. This emphatically supports the use of PARP inhibitors as first-line therapy. However, there seems to be a spectrum of benefit: people with *BRCA* mutations benefited the most, followed by people with HRD but no *BRCA* mutation, then people with neither. Only the PRIMA trial of niraparib showed a statistically significant benefit in the last group, and this was small at just under three months[9].

In April 2020, on the basis of these trials, the FDA approved the combination of olaparib and bevacizumab for first-line maintenance treatment of people with HRD. The EMA followed suit in November. Because the use of this treatment is no longer specific to just people with *BRCA* mutations, testing for HRD has emerged as another key battleground (see 'Testing times').

Niraparib, meanwhile, won approval from both the FDA and EMA for first-line maintenance in all patients — regardless of HRD status. This might seem to imply that niraparib performs better than other PARP inhibitors in people with tumours capable of homologous recombination. However, this conclusion should be treated with caution — differences in inclusion criteria and the control groups used in the trials of different PARP inhibitors make it difficult to directly compare their efficacy. "I doubt there's

Testing times

The combination of olaparib and bevacizumab as a first-line maintenance therapy, approved in 2020 following the PAOLA-1 trial, is available only to people who have tumours with homologous recombination deficiency (HRD), in which a mechanism for repairing double-strand DNA breaks is impaired. As a result, identifying the HRD status of tumours has grown in clinical importance.

Testing people for *BRCA* mutations, one cause of HRD, has been integrated into clinical practice since the advent of PARP inhibitors. Testing for HRD brought about by other means, however, is less established. Current tests are costly, and involve significant uncertainty. Many trials of PARP inhibitors, including PAOLA-1, have used a commercially available HRD test made by Myriad Genetics in Salt Lake City, Utah. The test uses sequencing to find *BRCA* mutations, and produces a 'genomic instability' score that is related to DNA damage. However, the threshold at which a score is said to show HRD is controversial. The VELIA trial used a slightly different value from PAOLA-1 — and reported slightly higher prevalence of HRD[10]. Current tests also falsely identify many patients as having no mutations, so are not reliable predictors of benefit from PARP inhibitors.

Multiple groups are working on better tests. Some efforts involve next-generation sequencing or gene transcription assays. Another approach is functional tests. "HRD is a functional term, but current tests don't measure function," says oncologist Daniela Matei at Northwestern University in Chicago, Illinois. "They measure mutation, or genomic scars." Tests that probe what cells actually do might be better suited to developing the real-time read-outs that would be invaluable for guiding treatment decisions. This will be important because the task of determining HRD status is complicated by cancer's inherent heterogeneity: one part of a tumour might be capable of homologous recombination whereas another is not. This is also likely to change in response to treatment, so in some cases determining HRD status will be a continuing task.

Oncologist Timothy Yap (right) with a colleague at the MD Anderson Cancer Center, Texas.

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any difference between the drugs," says Matei.

Differences in the molecular characteristics of the drugs cannot be entirely ruled out. For instance, a 2020 laboratory study suggested that the molecular conformations of PARP inhibitors help to determine the PARP-trapping strength[10]. However, this study's findings predict that olaparib would be stronger than niraparib – the opposite pattern to the trials.

Even if some PARP inhibitors are more effective than others, "the good news is we have options for patients", says Ray-Coquard. Being able to use them in first-line treatments might make all the difference. Comparing SOLO-1 with SOLO-2, progression-free survival increased by around 70% in both cases – but this amounts to 13 months in SOLO-2 (ref. 11), and 3 years in SOLO-1 (ref. 4). More options might be on the horizon. The ATHENA trial, testing rucaparib as a first-line maintenance treatment, is expected to reach primary completion by the end of 2024.

One drug for all

Now that PARP inhibitors are approved for both relapsed and newly diagnosed disease, a natural next step is to identify the benefit of giving a PARP inhibitor to someone whose cancer has relapsed after having already been given a PARP inhibitor. OReO is a phase III trial with olaparib that is designed to answer this question. The trial reported encouraging data in September at the European Society for Medical Oncology Congress. People with platinum-sensitive cancer seem to enjoy longer progression-free survival when receiving a second PARP inhibitor regardless of *BRCA* or HRD status.

It is important to note, however, that the OReO trial assessed people whose cancers relapsed after the initial treatment had ended; those whose tumours relapse during treatment with PARP inhibitors are unlikely to benefit from more of the same. Some people are resistant to the drugs from the start, and most others will ultimately find that their tumours become resistant. "For patients with both primary and acquired resistance, we have nothing that's targeted, that's approved, right now," says Timothy Yap, an oncologist at the University of Texas MD Anderson Cancer Center in Houston. "Their next choice is essentially chemotherapy, and we can do so much better than that."

"A proportion of these patients with *BRCA*-mutated tumours might even be cured."

Yap and other researchers are hoping that our understanding of the biology of DNA damage response can lead to the development of approaches that are more effective in a greater number of people. "We want more patients to respond," he says. "We also want responses to be deeper and more durable in each patient."

In an attempt to increase the magnitude of benefit, Yap is developing a more selective PARP inhibitor in collaboration with pharmaceutical company AstraZeneca in Cambridge, UK. "We're doing the trial currently with that agent," he says. "There's a lot of excitement about it." In addition to blocking PARP-1, current PARP inhibitors invariably block another PARP enzyme called PARP-2, but that might not be ideal. "We think a lot of the haematological toxicity is driven by PARP-2 inhibition," says Yap. "By dialling out the PARP-2, we can push up the doses of PARP-1 inhibition and get greater potency – and, hopefully, greater efficacy."

A strategy that could benefit more people, meanwhile, might be to confer some degree of HRD on cancer cells. For example, drugs that suppress BRCA proteins can mimic the impact of *BRCA* mutations. Researchers are also developing drugs that inhibit other components of the DNA repair machinery. "There are many exciting new agents that also target the DNA damage response, which are very distinct, with their own patient populations beyond *BRCA* mutated cancers," says Yap. "We're at the tip of the iceberg right now."

If used in combination with other DNA repair inhibitors, these drugs might help to combat resistance by making it harder for cancer cells to shift reliance between different repair mechanisms – a key goal for researchers. "It's all going to be about combinations," says Yap. Some studies have also suggested that combining PARP inhibitors with immunotherapy might be fruitful[12]. "That's launched several trials that are going to confirm that observation, or not," says Ursula Matulonis, an oncologist at Harvard Medical School in Boston, Massachusetts.

The treatment of ovarian cancer has already been irrevocably changed by PARP inhibitors, but there might be more advances to come. Having moved PARP inhibitors up to be used as first-line maintenance treatment, some researchers are wondering whether they could be moved up even further and given before chemotherapy – or even instead of it. The data to answer that question do not yet exist, but it would be best tested initially in people with *BRCA* mutations. "You'd want to try [it] in patients whose cancer is most sensitive," says Matulonis, although any clinical trial would have to be carefully designed, she adds, so as not to compromise care. Matei is also cautious about the potential cost of pushing on to this next level. "10–15% of patients who receive surgery and chemo are cured, so you don't want to lose that," she explains. "It's a difficult, but intriguing question."

Simon Makin is a science writer in London.

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