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Olaparib: the journey of a world-first drug

The pioneering cancer drug olaparib is a perfect example of how the ICR and The Royal Marsden take innovative science to patients. Here, we chart its evolution from laboratory concept to clinical treatment.

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When the drug olaparib was approved in Europe and the USA in 2014, it was a landmark moment for molecular medicine ? the first cancer treatment targeted against an inherited genetic fault to be licensed. Earlier this year, evidence followed that the drug could also benefit patients whose tumours have defects that are not inherited.

Scientists and clinicians at the ICR [6] and The Royal Marsden [7], supported by infrastructure from the BRC, were involved at every stage in the development of olaparib: discovering one of the genes it targets, developing the idea for a new approach to treatment, and running the clinical trials that proved its effectiveness. The drug has now been approved for women with ovarian cancer and inherited mutations to the BRCA breast cancer genes, and clinical trials are continuing in other groups of patients.

Professor Paul Workman, Chief Executive of the ICR, said: ?Olaparib is the first cancer drug to be approved that is directed against an inherited genetic mutation. Its development was underpinned by research carried out by scientists at the ICR, and represents a real scientific breakthrough. Larger clinical trials are ongoing, and we are confident that drugs like olaparib will become available for subgroups of women with ovarian cancer ? and ultimately patients with other cancers, too.?

> "The first licensed cancer drug directed against an inherited genetic mutation is a real breakthrough"
>
> *Professor Paul Workman, Chief Executive of the ICR*

The gene

For many years, scientists had suspected that breast cancer ran in families and were determined to find the genetic basis. In 1995, ICR researchers won the race to discover the second of two major breast cancer genes to be identified: BRCA2. Mutations in the BRCA2 gene greatly increase the carrier?s risk of developing not only breast cancer but also ovarian cancer in women and prostate cancer in men.

Its discovery has enabled families with a history of these cancers to be assessed for future risk and was a critical step in the development, 10 years later, of treatments such as olaparib for BRCA-associated cancers.

Cancer patients carrying BRCA mutations had strong, sustained responses when treated with olaparib

The idea

Professor Alan Ashworth, former Chief Executive of the ICR and one of the scientists who identified BRCA2, spotted an exciting opportunity to exploit the discovery for cancer treatment. His team had helped uncover the functions of the BRCA proteins and shown that they were normally used by our cells as one way of repairing faults in our DNA.

Professor Ashworth reasoned that cancer cells that lacked either BRCA1 or BRCA2 function might be highly sensitive to drugs that inhibit the molecule PARP ? another protein used to repair faulty DNA. In 2005, his research showed PARP inhibitors were indeed highly effective at killing cancer cells with BRCA mutations, opening the way for clinical trials at The Royal Marsden.

The drug

A series of drug trials ? led by Professor Stan Kaye and Professor Johann de Bono at the ICR and The Royal Marsden, and colleagues at Guy?s Hospital ? were launched to test whether PARP inhibitors such as olaparib could work as well in the clinic as they did in the laboratory. The early trials focused on patients with breast, ovarian and prostate cancers carrying BRCA mutations.

Despite the fact that these patients had undergone several previous rounds of chemotherapy that had failed to keep their cancers in check, a significant number had strong and sustained responses when treated with olaparib. The side-effects in patients treated with olaparib were relatively mild compared with conventional chemotherapy. Further trials, at The Royal Marsden and elsewhere, confirmed that PARP inhibitors were effective in BRCA-mutant patients.

Then, at the end of 2014, both the European Medicines Agency and the US Food and Drug Administration approved the use of olaparib in ovarian cancer patients with mutations in their BRCA1 or BRCA2 genes.

The future

We hope that the licensing of olaparib is the first step in it making a real difference to the lives of patients with ovarian cancer worldwide. But our researchers and clinicians are not stopping there, and are continuing to test the drug for benefits in other cancer types.

Earlier this year, the TOPARP Phase II trial, led by Professor de Bono, showed that olaparib could be effective in men with prostate cancer, including in some with gene defects in their tumours that were not inherited. It was the latest chapter in the evolving story of olaparib, and a perfect illustration of how the ICR and The Royal Marsden are together taking innovative science to patients.

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