The road to precision medicine.

Dec 2019 *Wendy Winnall, Scientific writer for PCFA*

Precision medicine for cancer means that the treatment most likely to help the patient is chosen based on test results. This approach is closer to reality for prostate cancer with exciting clinical trial results from 2019. The latest good news comes from a trial linking the benefits of Olaparib (Lynparza) with alterations in DNA repair genes.

For precision medicine to become a reality for prostate cancer we need two things: a choice of different medicines and accurate tests to identify the best one to use. We have a range of treatment options for men with advanced prostate cancer. What we need are biomarkers to identify the best one to use for each man. Biomarkers are things that we can test for such as proteins in the blood or urine or changes to specific genes. Potential biomarkers being tested for prostate cancer also include tumour cells or tumour DNA circulating in the blood.

Treatments for advanced prostate cancer

There is more than one treatment for men with advanced prostate cancer. These men have options such as various hormone therapies, different types of chemotherapy and drugs such as Enzalutamide (Xtandi) and Abiraterone (Zytiga). There are experimental and international therapies that some Australian men may also access. These include lutetium-177 PSMA, radium 223 (Xofigo) and Provenge (Sipuleucel-T).

Currently, treatment recommendations are made for men with advanced prostate cancer based on test results for features such as the stage and grade of the cancer, the number of tumours and their position in the body. Factors such as the preferences of the patient, other health conditions and the expected side effects also influence the treatment choice.

Unfortunately, not every treatment for advanced prostate cancer will slow tumour growth for each man with the disease. For treatments such as chemotherapy, it can take months to find out whether it is working. It would be ideal to know beforehand which treatment is most suitable. This would save men suffering side effects from a treatment that fails and from wasting precious time with such a treatment when another would have been better. Precision medicine is an approach that aims to improve these treatment choices.

Olaparib

There is much excitement about a new drug called Olaparib (Lynparza). Olaparib is a PARP inhibitor – a new class of cancer drug described in a recent research blog article. It's available in Australia for patients with ovarian, fallopian tube or peritoneal cancer, if they have a BRCA gene mutation. Availability for these cancers is possible because clinical trial evidence has demonstrated both safety and effectiveness for these specific tumour types. Olaparib is currently being testing in clinical trials for men with late-stage metastatic prostate cancer.

Olaparib kills cancer cells that are accumulating DNA damage due to defects in their DNA repair genes. Olaparib increases DNA damage. By doing this, it causes so many breaks in the DNA that the cancer cells can't repair them, so they die. This should only work in cells that already have DNA-repair defects, so the normal, non-cancerous cells are unaffected. It's an ingenious way to target cancer cells whilst protecting normal cells.

Since Olaparib should work best in tumours with DNA repair gene defects, this provides a possible method to find the men who would benefit from this treatment.

TOPARP-B trial

The TOPARP-B trial is the first trial to ask whether a genetic test can identify a group of men who will benefit from a specific treatment. In other words, this trial is testing a precision medicine use of Olaparib for men who test positive for specific gene defects.

This trial is testing the benefits of Olaparib for men with metastatic castration resistant prostate cancer. These men have tumours that have spread to distant sites and are no longer stopped by hormone therapy. Men joining the TOPARP-B trial had already tried chemotherapy for their cancer.

Men volunteering for the TOPARP-B trial started with a genetic test of their tumour DNA. 27% of these men had positive genetic tests. They had alterations in genes involved in repairing DNA damage such as BRCA1, BRCA2, ATM and CDK12. 18 different genes were included in the test. Only men who tested positive to one or more of these genes continued in the trial with Olaparib treatment.

TOPARP-B is a phase 2 trial that compares two groups of men having different doses of the drug. 49 men with positive genetic tests received 300mg Olaparib per day and 49 received 400mg per day. The aim was to ask whether their tumours responded to treatment. Responses to the drug included a reduction in tumour size on scans, a 50% decrease in PSA levels or a decrease in tumour cells circulating in the blood. The average follow-up time was just over 2 years.

The results were very promising. 54% of men having the higher dose and 39% having the lower dose saw their tumours responding to treatment.

As for all cancer drugs, Olaparib has many possible side effects. The most common serious side effect was anaemia (low red blood cells). Less serious issues included fatigue, back pain and nausea. One man died of a heart attack after 11 days taking the lower dose, an event that was possibly related to the treatment. The potential for serious side effects makes it all the more important that this treatment be offered to men who will most likely benefit from it. This important trial has shown that genetic tests for defects in a group of genes can be used to identify these men.

The TOPARP-B trial has shown that patients testing positive for DNA repair gene defects have a good chance of benefitting from treatment with Olaparib. Phase 3 trials showing an increase in survival times are needed for Olaparib to become available in Australia. The ongoing PROfound trial is one of numerous clinical trials that we hope will produce this important evidence.

If you are interested in reading the TOPARP-B scientific paper, you can find it freely available from The Lancet Oncology journal.