How do we overcome treatment resistance in a sarcoma cancer with already limited treatment options?

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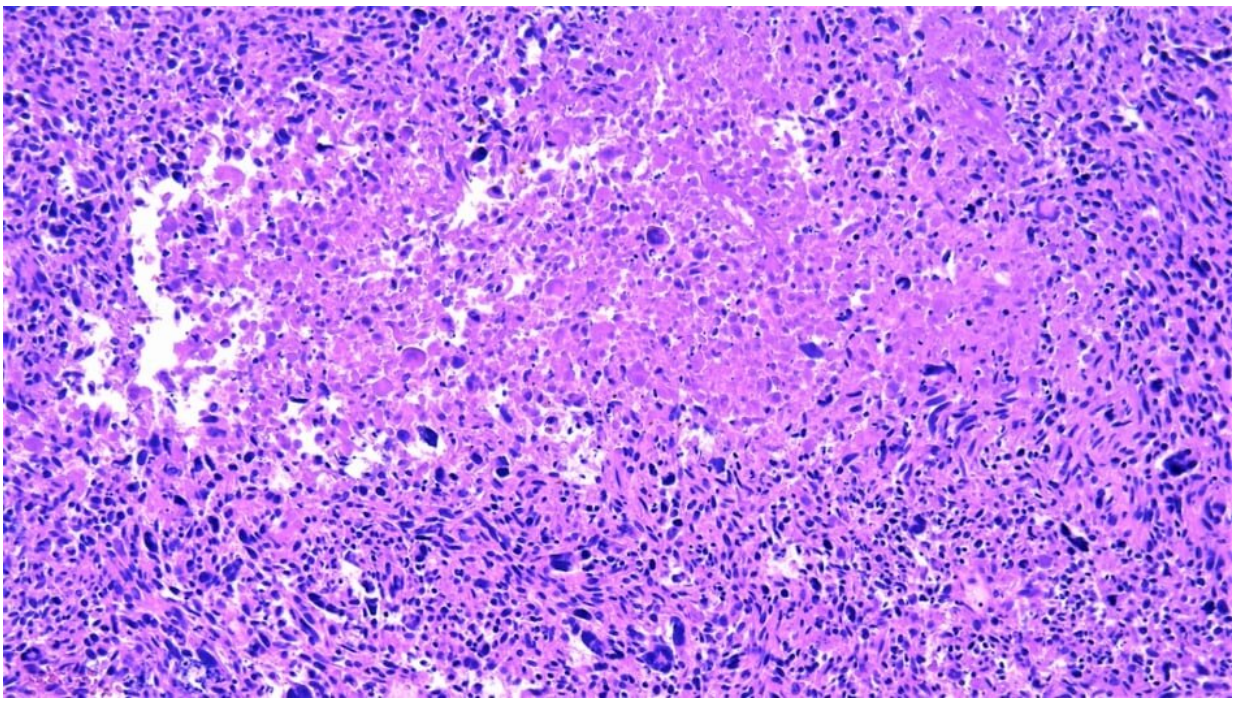

Histopathology image of leiomyosarcoma. Credit: Wikimedia Commons, CC-BY-SA 4.0

Leiomyosarcoma is a type of soft tissue sarcoma that is hard to treat and associated with a poor prognosis. Scientists at the Institute of Cancer Research are working to better understand the biology of this cancer to

develop more targeted and effective treatment options. Elena Daviter-Nowell spoke to Dr. Will Kerrison about the future of cancer treatment for patients with leiomyosarcoma.

Leiomyosarcoma is one of the most common sarcoma subtypes. It is a cancer that grows in smooth muscle cells, meaning it can develop anywhere in the body. There are often great differences between leiomyosarcoma tumors in individual patients so there can be a wide variety of clinical outcomes to treatments. Leiomyosarcomas are therefore hard-to-treat with few new therapies available and, sadly, a generally poor prognosis.

Through research, however, our understanding of the genetics and mechanisms of this disease is constantly improving, and new biomarker-driven therapies are being investigated that could help patients with leiomyosarcoma live longer.

Currently, standard treatment for leiomyosarcoma includes doxorubicin-based chemotherapy. A major challenge of using treatments such as chemotherapies is the build-up of toxicity within the body and the development of drug resistance by cancer cells.

This leads to progressively worse response rates if further chemotherapy treatment is required. Overcoming the mechanisms of drug resistance has been a priority for finding a highly effective therapy for patients with leiomyosarcoma, which could include the use of different therapies in combination.

Targeting leiomyosarcoma on different fronts

"A combination therapy describes a treatment where several drugs are used together to provide a combined, enhanced effect that gives a greater result than when each drug is used individually," explains Dr. Will

Kerrison, whose Ph.D. research into sarcomas was done in Dr. Paul Huang's Molecular and Systems Oncology team at The Institute of Cancer Research. Will is now a Postdoctoral Training Fellow in Professor Chris Lord's team at the ICR.

Will's Ph.D. research focused on developing models of soft tissue sarcoma that could be used for testing drugs to identify new treatments.

"Individual drugs all play important roles in targeting distinct cell pathways. When in combination, each drug has a different, independent effect—one drug working on one pathway that a cancer cell needs to survive, and another working on a different cell pathway to attack the cancer cell from different fronts."

There has been lots of research and many clinical trials assessing possible combination therapies. One such study showed that when two chemotherapy drugs were used together—doxorubicin and trabectedin—the median length of time before the disease progressed, known as progression-free survival, was more than a year, 12.2 months.

This was significantly higher compared to doxorubicin alone where median progression-free survival was 6.2 months. From this we can see how effective combination drugs can be and how they can provide much better outcomes than using therapies on their own.

Over the years, there has been extensive research on different chemotherapies and their use with other cancer drugs. However, though chemotherapy is very effective, it is also very toxic and there are often many destructive side effects. Recently, there has been an increase in research focusing on targeted therapy.

Targeted therapies focus on more precisely targeting cancer cells by acting on a fault found within them. The precision of targeted therapy

can mean significantly fewer side effects than chemotherapy and these drugs are considerably less toxic.

Kinder, more specific treatments for leiomyosarcoma

PARP inhibitors are a type of targeted cancer drug that have caused a breakthrough in cancer treatment over the last few decades, in part following the discovery of the breast cancer susceptibility gene, BRCA2 by ICR scientists in 1995.

PARP inhibitors, such as olaparib, block certain enzymes from repairing DNA damage in cancer cells, causing the cancer cells to die. As PARP inhibitors are targeted cancer drugs, they also cause significantly less damage to healthy cells than more traditional therapies such as chemotherapy.

Olaparib was developed following crucial involvement by ICR scientists, and it has been approved for use in BRCA1/2 mutated breast, prostate, ovarian, and pancreatic cancers. Other PARP inhibitors that have been approved for treatment in various cancer types include niraparib, rucaparib and talazoparib.

Early research has demonstrated that some types of leiomyosarcoma are sensitive to PARP inhibition, and there are a number of clinical trials now investigating these therapies in patients with soft tissue sarcoma, with early data from these studies showing promising results.

Future treatment of leiomyosarcoma

"We're starting to understand more about the biology of leiomyosarcoma and other soft tissue sarcomas and how we can use newer therapies, such as PARP inhibitors, to target its weaknesses," says Dr. Kerrison.

"However, our understanding of these drugs within this cancer type lags behind other types of cancers. For this reason, I believe that chemotherapy still has a massive role to play in treating patients with leiomyosarcoma. It may be that in the not-too-distant future, we'll be combining chemotherapy with PARP inhibitors to better treat leiomyosarcoma and give patients more time before their disease progresses," suggests Will.

"Our ultimate aim is to predict how a person's cancer will evolve resistance to treatment. By using new innovative tools to uncover the genetics of leiomyosarcoma and tailor treatment accordingly to prevent this from happening."

Predicting how leiomyosarcoma will evolve resistance to treatment

One way that we can predict how cancer may evolve resistance to treatment is by using biomarkers—biological measures, such as genes, proteins and other substances, that can be used to determine how well the body will respond to treatment.

Biomarkers help to maximize the effectiveness of a person's cancer treatment by indicating whether a patient is more or less likely to respond to a therapy—they can help clinicians know if there is something targetable in a person's cancer cells.

There are more than 50 different subtypes of soft tissue sarcomas and biomarkers already play an important role in diagnosing the diseases of patients. With the help of biomarkers, it will be easier to identify the subgroups of leiomyosarcoma patients that would benefit most from specific types of treatments, like PARP inhibitors.

"Leiomyosarcoma remains a challenging cancer to treat, but we have seen huge advances in our understanding of this rare cancer in the past few decades alone. Underpinning these advances is our emerging knowledge of the genetic alterations that drive disease progression and evolution of this complex disease," says Dr. Kerrison.

"Using this information, we can identify new drug targets and determine which patients would most benefit from different types of treatment. I am confident that, with our increasing knowledge of this rare disease through innovative tools and technologies, we can improve survival for patients with leiomyosarcoma."

Provided by Institute of Cancer Research

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