Targeting chemotherapy with genetic testing benefits women with aggressive breast cancer

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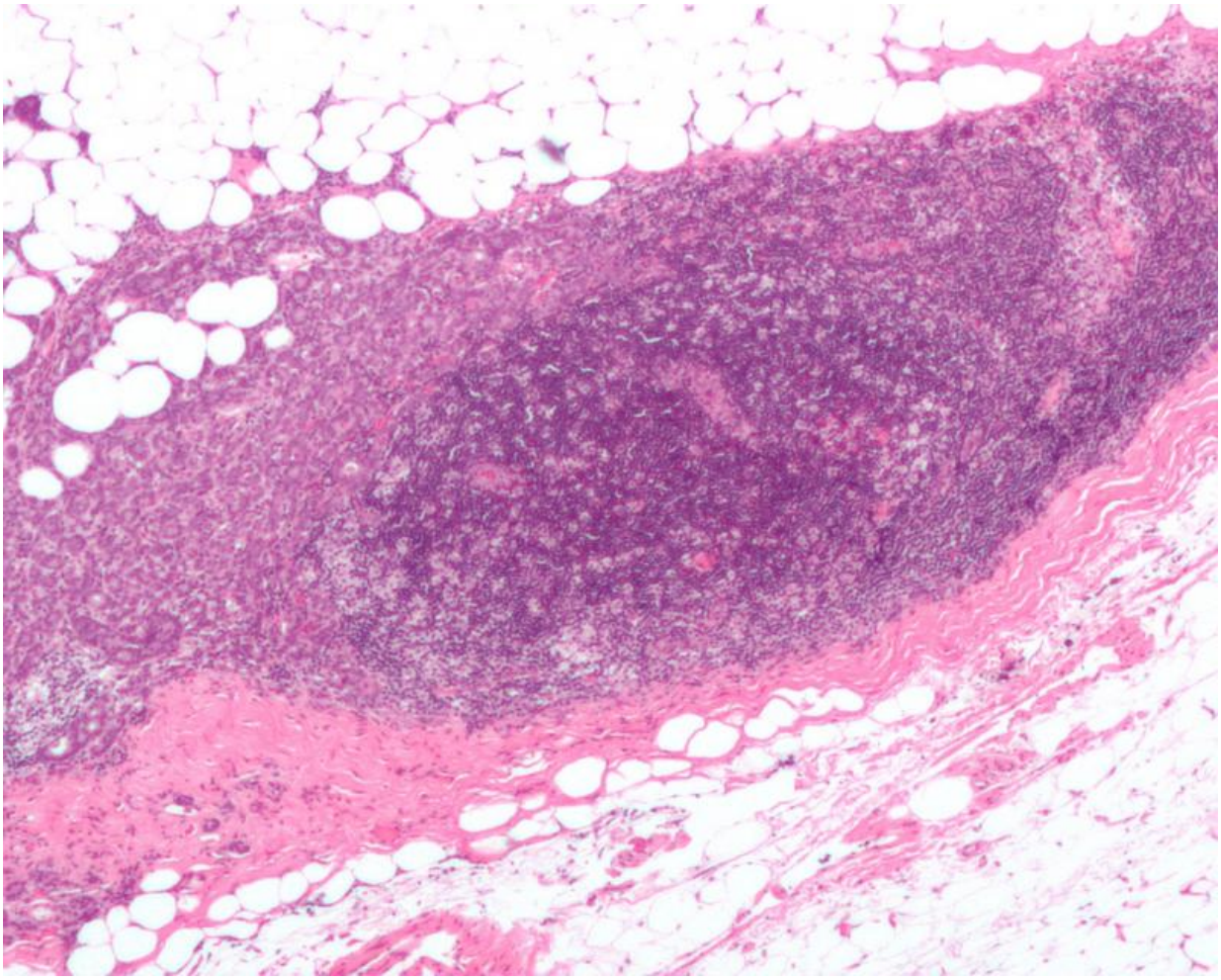

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Women with an aggressive form of breast cancer who have faults in their BRCA genes do much better on chemotherapy drug carboplatin than standard treatment, a major clinical trial reports.

Researchers found that women with advanced 'triple-negative' breast cancer who had inherited a BRCA mutation were twice as likely to benefit from carboplatin as docetaxel, which is currently standard of care for these patients.

The study was largely funded by both Breast Cancer Now and Cancer Research UK and led by a team at The Institute of Cancer Research, London, and King's College London.

The trial is set to change international clinical practice guidelines by ensuring that women with triple-negative breast cancer who are young or with a family history are considered for BRCA testing—so the best available treatment can be selected for them.

The study, published in the prestigious journal *Nature Medicine* today, was led by Professor Andrew Tutt in the Breast Cancer Now Toby Robins Research Centre at The Institute of Cancer Research (ICR) and the charity's Research Unit at King's College London, and Professor Judith Bliss in the Cancer Research UK-funded Clinical Trials and Statistics Unit at the ICR. It also involved hospitals around the UK.

Triple-negative breast cancer has limited treatment options because it doesn't respond to standard hormone therapies or targeted drugs like trastuzumab (Herceptin).

Advanced triple-negative breast cancer is usually treated with chemotherapy—but response rates remain low.

Researchers designed the trial to compare the effectiveness of docetaxel

with carboplatin—a drug co-discovered at the ICR—as these two treatments affect cancer cells in different ways. Carboplatin creates a specific form of damage to a tumour's DNA, exploiting a weakness in some triple-negative breast cancers' DNA repair machinery.

When analysing the response in the 376 women with advanced triple-negative breast cancer across the trial, regardless of BRCA gene status, the researchers found that the two drugs worked similarly well.

But among the 43 women in the study who also had BRCA gene faults, those who received carboplatin were twice as likely to respond to therapy as those given docetaxel.

In these women, tumours shrank in 68 per cent of the patients treated with carboplatin, but only 33 per cent of the women on docetaxel.

Carboplatin also had fewer side-effects and delayed tumour progression for longer in women with BRCA gene faults—stalling tumour growth for around seven months, compared with four months for docetaxel.

The researchers believe carboplatin is more effective for this patient group because it works by damaging tumour DNA—and BRCA mutations impair the ability of cancer cells to repair the type of DNA damage created by this kind of 'platinum' drug.

Professor Andrew Tutt, Professor of Breast Oncology at The Institute of Cancer Research, London, said:

"Our study has found that women with triple-negative breast cancer who have BRCA1 or 2 mutations are twice as likely to respond to carboplatin as they are to standard treatment. It strongly suggests that many women with triple-negative breast cancer should be considered for testing for faults in the BRCA genes so those who test positive can benefit from

carboplatin. Using this simple test enables us to guide treatment for women within this type of breast cancer. I am keen for these findings to be brought into the clinic as soon as possible.

"This is a great example of using personalised genetics to repurpose a chemotherapy drug into a targeted treatment, by understanding that its DNA-damaging effects might be particularly effective against cancer cells with deficiencies in DNA repair in appropriately selected patients."

Professor Judith Bliss, Director of the Clinical Trials and Statistics Unit at The Institute of Cancer Research, London, who led the management of the study, said:

"Women with triple-negative breast cancer often only survive for one to two years after the cancer has relapsed and spread to other parts of the body so there is an urgent need to find alternative treatments for this group of patients.

"Our study has shown that this doesn't have to mean developing new drugs. We can use existing—and often cheaper, generic—drugs more effectively by targeting treatment based on weaknesses in individual patients' tumours."

Baroness Delyth Morgan, Chief Executive at Breast Cancer Now, which co-funded the trial, said:

"This is a landmark and long-awaited step forward for women with incurable and aggressive breast cancers who carry BRCA mutations—who until now have had no targeted options to rely on.

"While a cornerstone treatment, chemotherapy can be a blunt tool for many, with side-effects that can be difficult to cope with. It is fantastic news that carboplatin will now offer a more effective, kinder and

targeted treatment to a group of patients who have long been in need of new hope. For those living with the impossible reality of incurable cancer, these precious extra months of better quality life before their condition worsens could mean absolutely everything.

"We hope future studies will now uncover whether this advance could benefit patients with early breast cancer too.

"We must now make sure this breakthrough reaches 'triple negative' patients that could benefit as quickly as possible. We urge NICE to include carboplatin in their guidelines on advanced breast cancer swiftly and NHS England to consider issuing commissioning advice to help ensure its routine adoption for these patients."

Neelam, who was a patient at The Royal Marsden when she took part in the TNT trial, said:

"I was diagnosed with metastatic triple negative breast cancer in early 2010 after finding a lump during a yoga class. I had treatment at The Royal Marsden, but sadly I found it had returned a year later, when I was diagnosed with lung metastasis. It was an incredibly difficult time for me; having cancer for the second time really shook me—especially the fact that it returned so quickly.

"I was determined to do anything I could to get treated, and luckily was able to take part in this trial. The support I had throughout from The Royal Marsden was second to none and with the regular check-ups that were required- it was like another 'tick' to say "I'm still here".

"Now, six years on, my scans show that I'm all clear of the disease. Its thanks to research like this, and The Royal Marsden who treated me, that I've been given a second chance of life."

Neelam, 57, started treatment under the TNT trial in October 2011 and finished in February 2012. She received carboplatin during the trial. She's remained disease free since finishing the trial.

More information: Carboplatin in BRCA1/2-mutated and triplenegative breast cancer BRCAness subgroups: the TNT Trial, *Nature Medicine* (2018). nature.com/articles/doi:10.1038/s41591-018-0009-7

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