Two-in-one drug combining Herceptin with chemotherapy keeps women's breast cancers at bay

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Guiding chemotherapy to a tumour by attaching it to the antibody-based target drug Herceptin (trastuzumab) is effective at treating women with breast cancer who have no other treatment options, a new clinical trial

shows.

The two-in-one treatment kept breast cancer at bay in women with a type of the disease called HER2-positive breast cancer who had stopped responding to existing drugs.

As well as being effective in women with high HER2 levels in their tumour, it was also active in a subset of women with lower levels of the HER2 protein who currently have no treatment options.

The new study, led by researchers at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, assessed the new treatment in patients for the first time, linking together the chemotherapy agent duocarmazine with trastuzumab—also known as Herceptin—which recognises the HER2 protein.

Women with HER2-positive breast cancer lived for 7.6 months after starting the treatment with no disease progression, whilst those with lower HER2 levels had progression-free survival of 4.9 months, showing that the drug extended life for patients who have run out of other treatment options.

The study was published today (Thursday) in *The Lancet Oncology* and funded by Synthon Biopharmaceuticals.

25 per cent of all breast cancers have higher than normal levels of HER2, which is a protein that plays a key role in the development of breast cancer. HER2-positive breast cancers are more aggressive and grow faster than some other subtypes.

HER2-positive breast cancer patients eventually develop resistance to standard therapies, leaving them with a poor prognosis and few further treatment options.

Therefore, scientists began exploring other approaches to deliver anti-cancer drugs to the tumours by linking chemotherapy drugs to an antibody.

The antibody acts as a guide for the attached drug, detecting the HER2 protein on the surface of the cancer cells. Once these two drugs—attached by a 'linker' to form the antibody drug conjugate—are internalised into the cancer cell, the linker is broken by enzymes within the cell to release the cytotoxic drug, resulting in DNA damage to the cancer cell. This approach allows the drug to be delivered directly to the target cancer cells.

As this method selectively targets the cancer cells, it minimises the damage done to the surrounding healthy cells, reducing toxicity and side effects in the patient.

The well-known breast cancer treatment Kadcyla is an example of this approach. Kadcyla is made up of the antibody trastuzumab linked to the chemotherapy drug emtansine.

However, HER2-positive cancers that are resistant both to trastuzumab alone and also to the trastuzumab-emtansine conjugate are becoming more common, again leaving these patients without further treatment options.

In this study, scientists linked trastuzumab with another chemotherapy drug, duocarmycin. When treated with this antibody-drug conjugate, on average breast cancer patients with high levels of HER2 in their tumour survived with no disease progression for more than seven extra months.

This indicates that by linking trastuzumab with a different chemotherapy drug—duocarmycin instead of emtansine—it was possible to overcome previous resistance to treatment.

Also, patients with breast cancer who had low levels of HER2 lived for nearly 5 months longer with no disease progression when treated with trastuzumab duocarmazine than they would have without the treatment.

This is an important finding as there are currently no approved HER2-targeting drugs or antibody-drug conjugate for low-HER2 breast cancer patients. This high unmet need could be met by the duocarmazine conjugate, potentially giving these patients life-extending options.

The researchers are hopeful that this approach could not only be used to treat breast cancer with high and low HER2 levels, but also to other cancer types with varying HER2 levels such as endometrial, urothelial and oesophageal cancer which have limited treatment options due to drug resistance and poor prognosis—although further studies are required to confirm this.

The late-phase TULIP trial is currently recruiting patients to looking into whether trastuzumab duocarmazine is more effective than the standard chemotherapy for women with HER2-postivie breast cancer.

First author Professor Udai Banerji, Deputy Director of the Drug Development Unit at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, said:

"The approach used in this study of combining the antibody and drug is a highly successful way of targeting tumours. With the antibody acting as a guide to find and target the cancer, the duocarmazine drug can be released directly to the tumour cells, destroying them whilst minimising the damage to surrounding healthy cells."

"Trastuzumab duocarmazine has shown promising anti-tumour activity in breast cancer patients with varying levels of the cancer-driving HER2 protein. As these cancers often develop resistance to the current standard

of care, this treatment could be extend the lives of patients who have otherwise run out of options."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"This trial shows that the innovative approach of linking antibodies to specifically target cancer cells with chemotherapy drugs to kill them is effective in patients who have developed resistance to other treatments.

"Drug resistance is a major challenge we face in getting cancer treatments to work. By adapting the technique of antibody-drug conjugates to overcome resistance to current treatments, the lives of patients can be extended to give them valuable time with friends and family.

"This research is part of the ICR's ambitious strategy to understand cancer's complexity and evolution—and to overcome evolution and drug resistance through the world's first 'Darwinian' drug programme."

Provided by Institute of Cancer Research