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Personalised therapies for treating metastasing breast cancer

Breast cancer is characterised by broad genetic diversity. Successful treatment is made even more difficult by the fact that, in advanced breast cancer, the properties of metastases often differ significantly from the primary tumour. The Heidelberg CATCH study is now collecting genetic profiles from patients' metastasis tissue samples, which can be used to tailor therapy to individual requirements. If necessary, therapy can subsequently be adapted to an even greater extent. The study aims to improve control rates in advanced metastatic breast cancer, delay disease progression and reduce the risk of side effects.

Prof. Dr. Peter Lichter (left), German Cancer Research Center, and Prof. Dr. Andreas Schneeweiss, National Centre for Tumor Diseases who run the Translational Breast Cancer Programme in Heidelberg

With an estimated 71,900 newly diagnosed cases in 2018, breast cancer is by far the most prevalent cancer in women in Germany. Around one in eight women are diagnosed with breast cancer during their lifetime. Although the mortality rate has fallen in recent decades, and although the majority of women affected can now be cured, invasive breast cancer (by far the most common type of malignant breast cancer) is still the leading cause of cancer deaths. It accounts for approximately 18,000 deaths in women per year. About 90 percent of these are the result of metastasis (statistics from the World Health Organisation and the Robert Koch Institute: Cancer in Germany, 2017).

As long as the tumour is small and confined to one breast (stage I), it can usually be completely cured. If the tumour has spread to the lymph nodes and/or other tissue surrounding the breast (stages II and III), the chance of recovery depends on the ability to completely remove the tumor tissue and destroy micrometastases. Advanced breast cancer, in which distant metastases have formed in other organs of the body (stage IV), is almost impossible to cure. In these cases, therapy is aimed at prolonged "progression-free survival" (PFS), i.e. stabilisation of the tumour disease associated with as good a quality of life as is possible in line with the patient's wishes (see figure).

Breast cancer diversity and metastases

Stages of invasive breast cancer and therapeutic targets at the National Centre for Tumour Diseases. [PFS: "progression-free survival" (see text)].

Breast cancer occurs in very heterogeneous forms. Histological criteria, i.e. the degree of differentiation (grading) and the expression of certain receptor proteins (oestrogen receptor alpha, progesterone receptor and growth factor receptor HER2) in the tumour cells are used to classify breast cancer subtypes. These subtypes differ greatly in disease progression and prognosis and must be treated differently. Genome sequencing and expression profile analyses show that every breast cancer is unique and differs from others in its molecular pattern. As part of a programme called COGNITION, researchers at the National Centre for Tumour Diseases (NCT) in Heidelberg are now establishing molecular genomic profiles in patients with early stage breast cancer, but with a high risk of metastasis, in order to be able to tailor therapy to the requirements of the individual patients. The programme began in early 2019 and is led by molecular geneticist Peter Lichter and medical oncologist Andreas Schneeweiss, and aims to reduce the risks of relapse and metastasis and increase the chances of recovery.

The Heidelberg CATCH study

The situation is even more complex in advanced breast cancer, when metastases are already visible. "We see greater differences not only between patients, but also between individual cancer cells in the same patient," explained Lichter. "That's why the treatment of metastatic breast cancer is so difficult." The molecular and genetic profiles of the primary tumour and

its metastases are quite different from one another. The Heidelberg Catch study ("Comprehensive Assessment of Clinical Features and Biomarkers To Identify Patients with Advanced or Metastatic Breast Cancer for Markers Driven Trials in Humans") will use biopsy material from the metastases of women with advanced breast cancer to identify biomarkers and target molecules of therapeutic agents as well as determine the molecular profile of the metastases on the DNA and RNA level ("whole genome sequencing and transcriptome sequencing").

Where possible, the molecular changes identified will be compared with the results of clinical trials and therapeutic interventions. Taking into account molecular reports and pathological findings, the NCT's Molecular Tumour Board consisting of treating physicians, pathologists, bioinformaticians, molecular biologists and human geneticists will then select a therapy according to the individual patient's requirements and with the patient's consent. Therapy can either be a standard form of therapy or what is called "off-label" therapy involving a pharmaceutically active agent that is approved for other diseases, but which appears to be promising based on the tumour's characteristics.

Another therapeutic option is to use an innovative therapeutic method that is still being tested or a combination of different therapeutic approaches. Schneeweiss emphasised: "One of the peculiarities of our study is that we not only have a wide range of therapies available, but we only include patients that we can treat here in our hospital. This means that genetic analysis and treatment happen alongside one another, and we can respond very quickly and adjust the therapy, depending on how the patient responds to treatment."

The first CATCH study patient was recruited in June 2017. By February 2019, 190 patients were enrolled, some of whom have undergone molecular stratification of the tumour, i.e. a personalised medicine approach used to divide individuals into different subgroups based on differences in the molecular characteristics and metastases of their tumours, and are treated with specific, sometimes combined therapies based on this approach. Even though it is still too early to evaluate the results of the study, Lichter and Schneeweiss were able to present some positive cases at a press workshop held at the German Cancer Research Center on 21st January 2019. "In patients who had no hope of improvement using a conventional treatment approach, the disease state had stabilised, and some even showed a tendency for partial metastasis remission. In some patients we were even able to achieve the progression-free extension of survival in combination with a high quality of life, which is a primary therapeutic goal of the CATCH study."

In future, it will also be necessary to carry out diagnoses of multiple biopsies, and potentially also do single-cell sequencing in order to be able to respond to altered tumour properties that may occur through clonal evolution during metastasis. However, there is hope that instead of using biopsy material, which has to be removed using complex procedures, it will soon be possible to use tumour DNA and tumour cells that circulate in the blood for the molecular analysis and monitoring of cancer diseases.

Article

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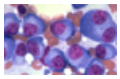

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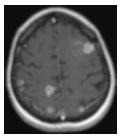

Tumour metastasis

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