Medications that target metastasing tumours

Tumour metastases are often resistant to the drug that is used to eliminate the primary tumour. Genome-wide analyses of mutation patterns in the primary tumour and its metastases provide information on the aggressiveness of cancer and may help to find the best available means of further treatment. This has been demonstrated by scientists from Heidelberg in a clinical trial on the molecular evolution of renal cancer.

Prof. Dr. rer. nat. Holger Sültmann, DKTK professor and director of the Department of Cancer Genome Research at DKFZ and NCT in Heidelberg.

With approximately 9,500 men and around 5,500 women diagnosed with renal cancer in Germany every year, this tumour is one of the less common types of cancer compared to breast, prostate, colon or lung cancer. The vast majority of renal tumours are clear cell renal cell carcinomas (ccRCC). Their outcome is specifically unfavourable when metastases have formed, which happens in about 30 percent of all patients with ccRCC. Since the introduction of targeted therapies – which are drugs that interfere with specific molecules such as growth factor receptors and signal transduction chains involved in cancer cell growth – the median survival of ccRCC patients with metastases has risen from nine to more than thirty months. "Metastatic renal cancer is easier to manage than it used to be," said geneticist Prof. Dr. rer. nat. Holger Sültmann from Heidelberg. "Even if the cancer cells become resistant to a cancer drug - which unfortunately is the case with most patients after a certain time – targeted therapies have a very favourable outcome when a suitable drug for treating a patient's tumour has been identified."

Molecular evolution of kidney cancer

Sültmann and colleagues from the German Consortium for Translational Cancer Research (DKTK) at

the German Cancer Research Center (DKFZ) and the National Center for Tumour Diseases (NCT) in Heidelberg are studying genome changes and gene expression in cancer cells. Since 2014, Prof. Sültmann, Dr. Carsten Grüllich, physician and scientist at the NCT, and other colleagues from the Heidelberg University Hospital have been involved in a clinical trial called MORE ("Molecular Renal Cancer Evolution") aimed at finding out which cancer drugs are suitable when tyrosine kinase inhibitors (TKIs) that are used as targeted metastising ccRCC therapies have lost their effectiveness. As the researchers report in the journal "Oncotarget," acquired TKI resistance is based on heterogeneous cells within the tumour, which metastasise as resistant subclones.

PD Dr. med. Carsten Grüllich, head of the Section of Translational Uro-Oncology, National Center for Tumour diseases, Heidelberg.
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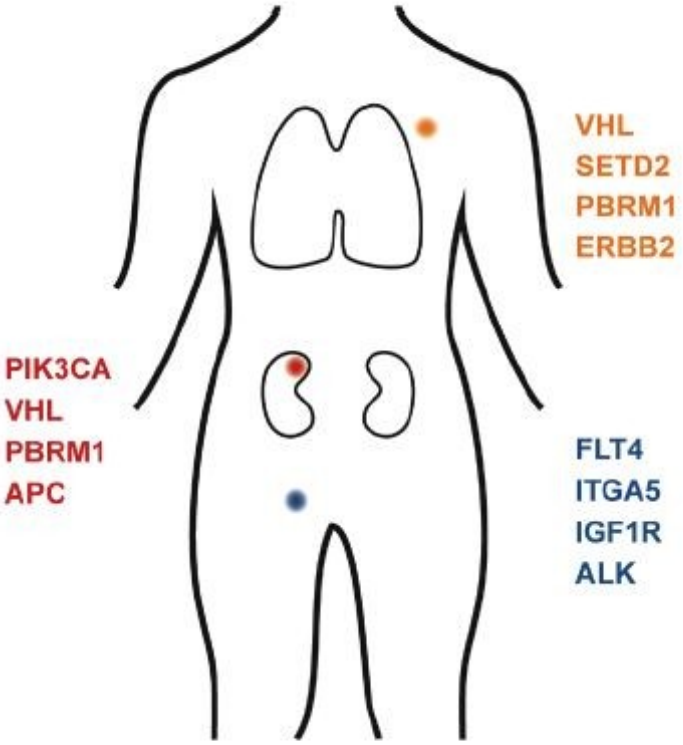
"MORE was the first trial that analysed not only the complete genetic profile of the original tumour in advanced renal cell carcinoma patients undergoing TKI therapy, but also that of the metastases that had developed in other organs," says Grüllich. Of the many hundreds of changes in the DNA sequence which the researchers were able to detect in the cancer cells, only a very small number was present in both primary and secondary tumours. For example, in a patient with metastases in the ilium and chest wall only three out of a total of 1,445 identified mutations were identical in both the primary tumour and metastases. In particular, the metastatic tumour in the chest wall had accumulated mutations in genes whose changes are associated with cancer growth, e.g. the tumour suppressor genes VHL and PBRM1, the epidermal growth factor receptor genes ERBB2 and the histone methyltransferase gene SETD2 (see figure below).

"Breast cancer genes" in kidney and prostate cancers

In the metastasic tumour of another patient, the scientists found a mutation in the BRCA1 gene that had not been present before treatment. BRCA1 is a tumour suppressor gene that encodes a protein that repairs double strand breaks in the DNA. It has become known as the "breast cancer gene" because women with mutations in this gene have a dramatically higher risk of developing breast cancer. Genetically modified BRCA1 and the closely related BRCA2 gene are also involved in the development of ovarian and prostate cancer, and possibly also in the pathogenesis of colon and pancreatic cancer. "A drug called olaparib is successfully used to treat some of these cancers. This drug prevents cancer cells from interfering with DNA repair, so that the cancer cells undergo programmed cell death," says Sültmann. Olaparib blocks poly-ADP-ribose polymerase (PARP), an enzyme involved in the repair of damaged DNA.

An interdisciplinary study led by Prof. Stefan Duensing, which also involved researchers from the



Mutation patterns identified in the primary tumour and in the metastases.
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Institute of Pathology at the Heidelberg University Hospital, the Department of Urology at the Heidelberg University Hospital and the NCT, has now demonstrated the efficacy of PARP inhibitors for treating prostate cancer in patients with defective BRCA1 or BRCA2 genes. "Patients with mutations in the BRCA1 and BRCA2 genes develop the tumour disease at a relatively young age. The disease progresses very rapidly and often has a fatal outcome," explains Duensing, head of the Section of Molecular Oncology at the Department of Urology at Heidelberg University Hospital. "Initial treatment of affected patients with a PARP inhibitor has not led to a cure, but has significantly improved the patients' quality of life." By analysing the mutations, prostate cancers can be divided into genomic groups with different disease progression for which different treatment options can be selected. At present, all patients with prostate cancer are usually treated in a similar way, but "in clinical practice, we have seen that the patients are actually significantly different, something we have suspected for a long time," Prof. Markus Hohenfellner, the medical director of the Department of Urology at Heidelberg University Hospital.

In principle, it is also worthwhile considering a PARP inhibitor therapy for renal cancer patients with BRCA1 gene mutations such as those identified in the MORE trial. However, Grüllich emphasised that in addition to targeted molecular therapies, further treatment options such as immunotherapy must also be taken into consideration. He also points out that the results of the current study now need to be confirmed in a larger patient population before the mutation patterns of metastases can become part of therapy planning.

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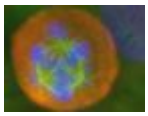

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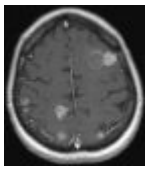

Tumour metastasis

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