Targeted therapeutic approaches that revolutionise melanoma treatment

Melanoma is difficult to treat once it has spread from the skin to other parts of the body. Classical chemotherapy is often ineffective and the majority of patients die within a few months after diagnosis. However, the biggest breakthrough in around 30 years has now been achieved with the development of kinase inhibitors that directly interfere with the cancer cells' molecular signalling pathways. Clinical research into the application of kinase inhibitors for the treatment of melanoma involves scientists from the Department of Dermatology at the University Hospital of Tübingen.

In Germany, around 15,000 people are diagnosed with melanoma skin cancer every year. The early stages of this cancer can be treated very effectively and the majority of patients can be cured by surgical removal of the tumour. However, cancer cells that have already spread into the lymph nodes or other organs reduce life expectancy to under a year. "The type of chemotherapy that has been standard treatment since 1975 only has a positive effect in a very small proportion of patients," said Professor Dr. med. Claus Garbe who heads up the Centre of Dermato-Oncology (ZDO) at the University Hospital of Tübingen.

A new era in melanoma skin cancer treatment has begun with the development of new drugs that are able to selectively inhibit the molecular signalling pathways in tumours. "As is the case with all other tumours, the accumulation of genetic modifications also lead to the pathogenesis of melanoma; the pigment cells degenerate and turn into tumour cells," said Garbe. Aberrant regulation of mitogen-activated protein kinase (MAPK) cascades plays a key role in the development of melanoma and other human diseases. The MAPK signalling network involves the protein kinases RAS, RAF, MEK and ERK and regulates cell growth and survival.

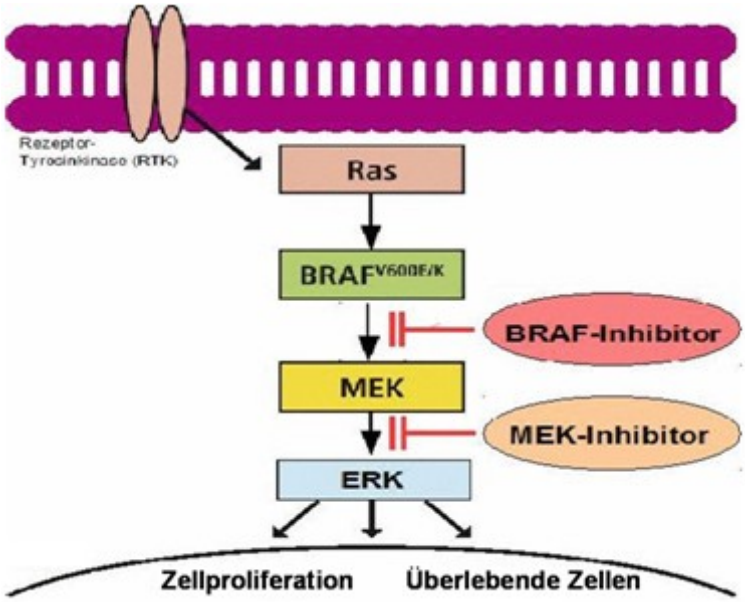
Specific blockage

Prof. Claus Garbe

“Around 50% of melanomas harbour BRAF mutations; BRAF is an RAF kinase isoform,” said Garbe. Most of them carry the V600 mutation. The V600 mutation leads to an amino acid exchange in the BRAF protein. The kinase activity of the mutated BRAF protein is 800 times higher, which leads to the overactivation of the MAPK signalling pathway. The affected cells begin behaving independently from growth factors and divide in an uncontrolled manner. “This type of mutation is also referred to as a driver mutation, i.e. a mutation that basically pushes cells to become cancerous,” Garbe says.

The new drug, vemurafenib, works by specifically inhibiting the MAPK signalling pathway in the mutated form of the BRAF gene. In a clinical trial carried out in 2011 in which Garbe was involved, the kinase inhibitor vemurafenib had such an impressive effect that the trial was stopped early in order to put all the study participants on vemurafenib. “An intermediate analysis showed that patients treated with traditional drugs died a lot earlier and suffered stronger adverse drug effects than patients treated with vemurafenib, which is why all study participants were switched to vemurafenib immediately after the results were made available,” Garbe said. Vemurafenib was approved in Europe in February 2012 for the monotherapy of adult patients with melanomas that could not be removed surgically or had already spread to other organs and are characterised by a BRAF V600 mutation.

Longer lifespan and better quality of life



The MAPK signalling pathway plays a key role in the pathogenesis of malignant melanoma.
© modified from Dietel et al., Pathologe 2012

The clinical study showed that vemurafenib extended life and reduced the risk of the disease worsening. “In contrast to the two months that melanoma patients survive when undergoing chemotherapy, patients treated with vemurafenib survive for around five months,” Garbe said. The median survival of six to nine months was extended to more than 18 months. “It seems that a drug that selectively targets the V600 mutation is able to halt the progression of the disease,” Garbe explains. Although a long-lasting effect cannot yet be achieved, the results nevertheless give a completely new perspective to cancer therapy. “In future, the treatment of patients will depend a lot more than it does now on the molecular signature of the tumour, which is already pointing in the direction of personalised medicine,” says Garbe. Vemurafenib not only extends life and reduces the risk of the disease worsening, it also dramatically increases quality of life. Even patients with advanced melanoma skin cancer and reduced general conditions respond to the therapy within a

relatively short period of time with a considerable improvement in tumour-associated disorders. The melanomas and metastases shrink and even severe pain disappears. “Vemurafenib is the biggest breakthrough of all melanoma therapies so far,” said Garbe, visibly enthusiastic about the results. A second BRAF inhibitor – dabrafenib – has since undergone clinical testing and has already produced positive results.

More promising kinases in the pipeline

This said, BRAF inhibitors alone are not able to cure melanoma skin cancers. Although the substances achieve a 50% response rate, which is much higher than chemotherapy can achieve, the tumour nevertheless recurs sooner or later and grows and spreads again. “It appears that after some time the tumour cells somehow manage to accumulate mutations in other kinases and I assume that they circumvent the drug-mediated inhibition of the MAPK signalling pathway,” says Garbe.

The researchers therefore have high hopes for the development of novel kinase inhibitors with new targets. For example, the drug trametinib also targets the MAPK signalling pathway. However, in contrast to vemurafenib, rather than inhibiting mutated BRAF, it inhibits the MEK kinase, which is located further downstream in the MAPK signalling network. In a recent paper in the New England Journal of Medicine, Garbe and his colleagues showed that trametinib is also able to temporarily stop tumour growth. “The efficacy and effect duration of the MEK inhibitor is fairly similar to that of the BRAF inhibitor,” Garbe says.

Quantum leap in melanoma treatment

As both kinase inhibitors interrupt the same signalling chain, the researchers considered combining the two drugs. Another study, also published in the New England Journal of Medicine in 2012, showed that the simultaneous administration of BRAF and MEK inhibitors extended the median progression-free survival of patients to between 11 and 12 months. “This is a real quantum leap compared to what traditional chemotherapy is able to achieve,” Garbe says.

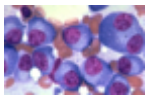
At least as spectacular as the finding that the combination of the two drugs delays the development of drug resistance is the fact that the novel treatment does not lead to previously observed adverse drug effects or at least reduces their occurrence. “Around 25% of all patients treated with a single BRAF inhibitor develop secondary tumours that arise in organs with a squamous epithelium within a few weeks after treatment. Although these tumours can be removed easily, they are nevertheless uncomfortable and cause emotional stress for the patients,” says Garbe. The combination therapy hardly ever leads to the development of such secondary tumours. Garbe and his team find this very encouraging. “It was basically the first time that we observed that the combination of two highly effective anti-cancer drugs leads to fewer adverse effects than each drug on its own.”

Further information:
Prof. Dr. med. Claus Garbe
Centre of Dermato-Oncology
Department of Dermatology
University of Tübingen
Liebermeisterstraße 25
72076 Tübingen
Tel.: +49 (0)7071/ 29 - 87 110
E-mail: claus.garbe(at)med.uni-tuebingen.de

Article

03-Dec-2012
sb (07.11.2012)
BioRegio STERN

The article is part of the following dossiers



Cancer therapy and cancer diagnostics