TARGETED THERAPIES

Imatinib is not effective in uveal melanoma

The receptor tyrosine kinase KIT and its ligand, stem cell factor (SCF), regulate a number of human cells, including melanocytes. The KIT protein is considered as a potential target for melanoma therapy with the tyrosine kinase inhibitor, imatinib. Uveal melanoma lacks activating mutations in the *BRAF* or *NRAS* genes, and is the most common intraocular tumor in Caucasian adults—with an incidence rate of 0.7 per 100,000 people. Uta Hofmann and colleagues investigated the expression of KIT and its ligand, SCF, in primary uveal melanoma and uveal melanoma metastases, and screened these samples for *KIT* mutations; the researchers also assessed the efficacy of imatinib in patients with uveal melanoma and found that KIT and its ligand are overexpressed in primary and metastatic uveal melanoma, but that imatinib was not clinically efficacious in this group of patients.

Eligible patients were aged 18 years or older with histologically confirmed metastatic uveal melanoma. A two-stage design was used to ensure that the number of patients exposed to an ineffective drug was kept to a minimum. The primary end point of the study was overall response rate.

Immunohistochemistry revealed SCF-positive tumor cells in 43% of primary

uveal melanomas and 58% of uveal melanoma metastases. The researchers noted strong expression of KIT in 55% of primary uveal melanomas and 76% of corresponding metastatic uveal melanomas. This overexpression suggested that imatinib could be clinically applicable in uveal melanoma metastases; this was tested in a group of patients who were assigned to receive imatinib 600 mg daily until a response was observed. However, no response was observed and therefore this study was stopped at the first stage. Subsequent further molecular analysis showed no mutations in the genomic sequence of *KIT* in exons 11, 13, 17 and 18. The MAPK pathway was not activated in any of the tumors, as measured by assessment of ERK phosphorylation. The authors conclude that despite the high expression of KIT and SCF, the absence of ERK phosphorylation might explain the lack of clinical effectiveness of imatinib in these tumors—which was unexpected owing to the high levels of the imatinib target KIT.

Mandy Aujla

Original article Hofmann, U. B. *et al.* Overexpression of the KIT/SCF in uveal melanoma does not translate into clinical efficacy of imatinib mesylate. *Clin. Cancer Res.* **15**, 324–329 (2009).