Towards personalised medicine for cancer

From initial therapy to follow-up

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This dissertation is divided in three parts. A general summary on the three large themes that are addressed in these parts is provided in **chapter one**. The first part, encompassing **chapters two through eight**, discusses the role and effects of mutations in the genes encoding for isocitrate dehydrogenase 1 and 2 (IDH1/2) in the biology of human cancer. These mutations occur in various types of neoplasms, such as glioblastoma, cholangiocarcinoma, chondrosarcoma, acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS). **Chapter two** is a general introduction of these mutations and their consequences on the biochemical, molecular and cellular level. Special attention is provided to the putative mechanisms via which IDH1/2 mutations contribute to the formation of cancer (oncogenesis), as well as their role in changing cellular metabolism. **Chapter three** describes the changes in cellular metabolism between IDH1/2 wild-type and IDH1/2-mutated glioblastoma at a more detailed level. Results from a data mining effort using The Cancer Genome Atlas and preclinical data obtained with IDH1/2-mutated and IDH1/2 wild-type cell models are discussed. **Chapter four** describes a technique called "metabolic mapping", which can be used to visualise and quantify the activity of enzymes, including IDH1 and IDH2, in cells and tissues. **Chapter five** describes results from the application of metabolic mapping and other interrogation techniques of cellular metabolism in human glioblastoma tissue. A major finding is that IDH1/2-mutated cells may use high levels of glutamate in their metabolism and that glutamate-providing enzymes but not glutamine-providing enzymes should be targeted for therapy. **Chapter six** reviews how the increased need for glutamate may lead to a more invasive growth pattern of IDH1/2-mutated glioma, as compared to IDH1/2 wild-type glioma. In **chapter seven**, inhibitors of glutamine and glutamate metabolism, such as metformin and chloroquine, are studied in cell models of chondrosarcoma and shows that cells of IDH1/2-mutated are not more sensitive to these drugs than cells of IDH1/2 wild-type chondrosarcoma, probably due to differences in IDH1/2-mutated chondrosarcoma versus other types of cancer that are frequently affected by IDH1/2 mutations. **Chapter eight** describes a study protocol of a phase I/II clinical trial of metformin and chloroquine in patients with IDH1/2-mutated glioblastoma, cholangiocarcinoma or chondrosarcoma.

The second part, encompassing **chapters nine through fifteen**, of this thesis discusses the effects of IDH1/2 mutations on the response of cancers to cytotoxic therapy. An introductory review on this subject is provided in **chapter nine**. In **chapter ten**, we show that patients with IDH1/2-mutated AML or MDS have shorter overall survival than those with IDH1/2 wild-type AML or MDS and that this is especially true for AML/MDS patients with the IDH1/2 mutation as the first occurring mutation. In **chapters eleven and twelve**, we show that the opposite is true for glioblastoma and low-grade glioma, where patients with IDH1/2 mutations have a prolonged overall survival as compared to IDH1/2 wild-type counterparts and that IDH1/2 mutations are a robust marker for prolonged prognosis. In **chapter thirteen**, we provide a potential explanation for the prolonged survival of IDH1/2-mutated glioblastoma patients, as compared to IDH1/2 wild-type glioblastoma patients: IDH1/2 mutations sensitise glioma cells to irradiation, a therapeutic modality that is part of the standard of care of glioblastoma. Via this mechanism, an improved response to this therapy at the cellular level may translate to prolonged survival at the patient level. In **chapter fourteen**, we show that IDH1/2-mutated AML cells have increased levels of DNA damage and can therefore be targeted by a relatively new class of drugs, the so-called PARP inhibitors. In **chapter fifteen**, we report differences in the genetic mutations occurring in AML/MDS that arose “spontaneously”, and the genetic mutations occurring in AML/MDS that may have been induced by previous chemotherapy or radiotherapy for an unrelated first cancer. The first group has the highest proportion of IDH1/2 mutations, whereas the second group, which is also called “therapy-related AML/MDS” has the lowest proportion of IDH1/2 mutations. This suggests that IDH1/2-mutated AML/MDS cells are generally not therapy-related. In turn, this data may represent further support that IDH1/2-mutated AML/MDS
Summary

cells are more sensitive to chemotherapy or radiotherapy. Why this is putative sensitisation to chemotherapy is not translated to a prolonged patient survival in IDH1/2-mutated AML/MDS is still unknown.

The third part of this thesis, encompassing chapters sixteen through twenty-three, discusses the early and late adverse effects of radiotherapy, including the induction of the aforementioned therapy-related AML/MDS. Chapter sixteen is an introductory review on this subject and discusses how a specific part of the bone marrow called "the bone marrow niche" can contribute to the formation of a therapy-related AML/MDS after chemotherapy and radiotherapy. Chapter seventeen describes a novel methodology to calculate the risk for the development of a therapy-related AML/MDS after radiotherapy, using publicly available national cancer registries such as the SEER registry by the National Cancer Institute of the United States. In chapter eighteen and nineteen, this methodology is used to describe increased risks for the development of therapy-related AML/MDS after treatment of thyroid cancer using radioactive iodine. There is no evidence for clinical benefit of this therapeutic modality in low-risk and intermediate-risk thyroid cancer, but it is still widely used because it is regarded as safe. We show that, although the absolute risks are small, radioactive iodine is associated with increased risks for the development of therapy-related AML/MDS. In chapter twenty, we show that there is a relation between the size of a breast tumour, the use of radiotherapy and the risk to develop a therapy-related AML, which may be related to high exposure of the bone marrow to radiation in radiotherapy for large breast tumours. In chapter twenty-one, we show that the risk for developing therapy-related AML/MDS is high in patients who received radiotherapy for any first type of cancer when they were an adolescent or young adult (15-39 years). In chapter twenty-two we show that in contemporary cohorts, there are no increased risks for the development of a glioma after radiotherapy in the same population of young patients. In chapter twenty-three, another type of adverse effect of radiotherapy is studied, namely cardiotoxicity to the heart after radiotherapy for oesophageal cancer. The explanation for this may be that the oesophagus lies directly adjacent to the heart and therefore the heart may be exposed to toxic doses of ionizing radiation during radiotherapy for oesophageal cancer.

The last chapter in this thesis, chapter twenty-four, is a general discussion on the studies described in this thesis and their place within the broader context of cancer research.