Towards personalised medicine for cancer

*From initial therapy to follow-up*

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Chapter 1: General introduction

Cancer is the second leading cause of death worldwide next to cardiovascular diseases. In 2015, 17.5 million people were diagnosed with cancer and 8.7 million people died of cancer. Those numbers emphasise that cancer is still a major challenge to humankind left to be tackled, but significant progression has been made in the last decades. The advent of next-generation sequencing has aided in the elucidation of the molecular basis of cancer. This has transformed our understanding of cancer as a molecular "black box" with a limited number of known molecular drivers, to a situation where we have insight in the genome-wide mutational and transcriptional landscape that characterises almost every tumour type, their various aetiologies and even their individual cells.

These advances have facilitated recent developments in personalised medicine, of which a prime example is the discovery of mutations in the genes IDH1 and IDH2 in cancer, encoding for the housekeeping enzymes isocitrate dehydrogenase 1 and 2. Recurrent mutations in these genes were first discovered in 2008 using whole-exome sequencing of glioblastoma specimens, the most common and most aggressive primary malignant tumour of the brain. Only one year later, it was reported that the mutant forms of these enzymes catalyse a neomorphic reaction which produces a novel metabolite that is normally present only in trace amounts in cells. Three years later, the first small-molecule drugs were developed that inhibit this neomorphic reaction and recently, less than nine years after the first publication on IDH1/2 mutations in cancer, an inhibitor of mutant IDH2 received FDA approval for the treatment of relapsed or refractory acute myeloid leukaemia (AML). This rapid trajectory between target discovery and drug approval emphasises the potential of contemporary cancer research to improve antineoplastic treatment and, ultimately, to find cures by means of individualised therapies for cancer patients.

Part 1 of this dissertation describes studies on the role of IDH1 and IDH2 mutations in cancer biology, with a focus on how the mutations change the metabolic processes of cancer cells. This phenomenon, also called metabolic rewiring, may contribute to cancer propagation but also creates profound differences between the metabolism of cancer cells and that of healthy cells. When these metabolic alterations cause a specific dependency of IDH1/2-mutated cancer cells on a metabolic process, it may result in a metabolic vulnerability that can be therapeutically targeted.

Part 2 discusses the association between IDH1/2 mutations in neoplasms and prolonged patient survival relative to wild-type IDH1/2 neoplasms, which has been described most thoroughly for glioma and specifically glioblastoma. We hypothesised that prolonged survival is caused by virtue of better therapy responses of IDH1/2-mutated glioblastoma compared to IDH1/2 wild-type glioblastoma and we discuss the implications of these findings in the context of the application of IDH1/2-mutant inhibitors. Furthermore, we show the relationship between IDH1/2 mutations and therapy sensitisation in the context of AML. Finally, we describe the mutational signatures of myeloid neoplasms, such as AML, that either arose de novo or developed after cytotoxic treatment of an unrelated first cancer. This phenomenon is also known as a therapy-related myeloid neoplasm (t-MN), which displays differences in the occurrence of IDH1/2 mutations as compared to myeloid neoplasms that arise de novo.

Part 3 elaborates on these aforementioned t-MN on a population scale in epidemiological studies. Radiotherapy and chemotherapy are still cornerstones of the treatment of nearly all types of cancer, but these cytotoxic therapeutic modalities also have significant short-term and long-term complications. One of the most devastating long-term adverse events associated with cytotoxic therapies is the formation of therapy-related cancer, of which t-MNs are the most notorious because of their frequent occurrence and dismal prognosis. This dissertation includes population-based
studies on the risks of t-MN after cytotoxic therapy in a situation where cytotoxic therapy is generally considered to be safe but at the same time there is limited clinical evidence for its efficacy (i.e. in well-differentiated thyroid cancer), in a situation where the cytotoxic therapy is needed most but confers the highest additive risk of t-MN (i.e. in adolescents and young adults), and in a situation where recent therapeutic developments aid in lowering doses of cytotoxic therapy, so that t-MN risks can be reduced as well (i.e. breast cancer). Several other late effects of chemotherapy and/or radiotherapy are also discussed in the chapters that belong to part 3.

Overall, the studies described in the present dissertation are aimed at the improvement of personalised medicine strategies for various types of cancer. The studies in parts 1 and 2 describe potential novel therapeutic avenues to treat \( IDH1/2 \)-mutated cancers and the conditions in which they may have optimal effects. The studies described in part 3 may improve risk/benefit assessments for the application of cytotoxic therapies in an individual patient, and the follow-up after the administration of such cytotoxic therapies. These nuances may ultimately improve personalised treatment and management of cancer.