Targeted therapy in oncology: mechanisms and toxicity

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General introduction and outline of the thesis

Cancer is one of the leading causes of death in developed countries, responsible for about 25% of all deaths. On a yearly basis, 0.5% of the population is diagnosed with cancer. Treatment options include surgery, radiotherapy and systemic therapies such as chemotherapy, endocrine therapy and targeted agents. These targeted anti cancer therapies include monoclonal antibodies and small molecules, for example tyrosine kinase inhibitors.

Conventional chemotherapeutical agents act by creating toxic effects on all dividing cells. This frequently results in in severe damage of normal tissues leading to side effects like myelosuppression, alopecia, and gastrointestinal problems. The optimum goal is to find a treatment modality that specifically kills malignant cells and causes little or no side effects.

This thesis focuses on targeted anticancer agents. An important class of these agents are the tyrosine kinase inhibitors (TKIs). One of the first steps in TKI treatment development is defining whether a specific type of cancer, for example the sarcomas in chapter 3 of this thesis, express the receptors that are targeted. Once a TKI is developed, phase I studies are conducted to characterize the safety and side effects of the drug when administered to patients. When relevant side effects emerge, studies investigating the underlying mechanisms leading to these side effects are called for. Also pharmacogenetic studies can be performed to investigate whether certain heritable genetic variations influence efficacy or safety of the drug. After the phase I studies have proven the drug to be safe, the drug can be further developed. This includes the investigation of the TKI when combined with other anticancer agents. Items of all the described steps in TKI development are described in this thesis.

In **Chapter 2,** recent developments of small molecule TKIs in the treatment of solid tumors are reviewed. These therapies were developed to target key elements that play a role in tumor development and tumor growth. Hormonal therapy in breast cancer is probably the oldest targeted therapy known in oncology. A more recent discovery is the class of drugs designated as tyrosine kinase inhibitors, developed to block intracellular signaling pathways in tumor cells, leading to dysregulation of key cell functions such as proliferation and differentiation.

In this chapter the following TKIs are reviewed: imatinib (Gleevec®/Glivec®), gefitinib (Iressa®), erlotinib (OSI-774, Tarceva®), lapatinib (GW-572016, Tykerb®, Tyverb®), canertinib (CI-1033), sunitinib (SU 11248, Sutent®), vandetanib (ZD6474, Zactima®), vatalanib (PTK787/ZK 222584), sorafenib (Bay 43-9006, Nexavar®), and Leflunomide (SU101, Arava®). Clinical studies with these new targeted agents in a wide range of tumor types and their future role in anticancer treatment is discussed.

Overexpression of the epidermal growth factor receptors EGFR and ERBB2 (Her2neu) is a negative prognostic factor in a variety of malignancies, including breast cancer, ovarian cancer, and lung cancer. These receptors constitute interesting drug targets. Indeed, drugs such as erlotinib, cetuximab and trastuzumab were developed specifically to inhibit these targets. In various subtypes of sarcomas, EGFR and ERBB2 overexpression has been reported and therefore drugs targeting these receptors may potentially be useful in the treatment of sarcomas. This is important because most sarcomas are relatively resistant to chemotherapy and novel treatments are urgently called for. Therefore, in **Chapter 3** we describe the construction of a tissue micro-array with 18 different types of soft tissue tumors to evaluate EGFR and ERBB2 expression.

The development and registration of new small molecule kinase inhibitors is proceeding remarkably fast. In this thesis, 2 phase I studies of new agents and 1 combination study of a new agent with a registered agent are described. The main objective of these studies is to evaluate the safety and tolerability of the new drug, with additional pharmacokinetic, pharmacodynamic and efficacy assessments. In **Chapter 4,** a phase I dose escalation study of telatinib (BAY 57-9352), a tyrosine kinase inhibitor of VEGFR-2, VEGFR-3, PDGFR-β and c-Kit, in patients with advanced or metastatic solid tumors is discussed. In **Chapter 9,** a phase I pharmacokinetic and pharmacodynamic study of the aurora kinase inhibitor danusertib (PHA-739358) in similar patients is discussed. In **Chapter 8** the use of a targeted agent in combination with a conventional chemotherapeutic drug is investigated. This study aims at enhancing the efficacy of the combination compared to monotherapy with each of these drugs, without causing more toxicity. In this phase I dose escalation study, treatment with sunitinib in combination with ifosfamide is studied.

With the development of new drugs new side effects may emerge. Vascular endothelial growth factor (VEGF) inhibitors induce hypertension as a common side effect. The mechanisms leading to the increase in blood pressure during this anti-angiogenic therapy are not clear. We hypothesized that systemic inhibition of VEGF impairs vascular function and causes rarefaction, which then leads to the development of hypertension in patients treated with anti-angiogenic agents. Functional rarefaction (a decrease in perfused microvessels) or anatomic rarefaction (a reduction in capillary density) may be the underlying mechanism.

We performed blood pressure and vascular structure and function studies in patients treated with VEGF inhibitors in order to clarify the mechanism by which small molecule angiogenesis inhibitors cause an increase in blood pressure. In **Chapter 6** the blood pressure and vascular studies during treatment with telatinib, a small molecule VEGF in-

hibitor, are described. In **Chapter 7,** the underlying mechanisms of hypertension related to bevacizumab (Avastin®), a VEGF antibody, are investigated.

Many studies have been performed to individualize anticancer drug treatment aiming at decreasing side effects or optimizing efficacy. Pharmacogenomics is a very exciting and new field of today's medicine, promising a personalized, tailor-made medication strategy to improve drug response and decrease harmful adverse reactions. Pharmacogenomics, often used synonymously with pharmacogenetics, is defined as: 'the individualization of drug therapy through medication selection or dose adjustment based upon direct (e.g., genotyping) or indirect (e.g., phenotyping) assessment of a person's genetic constitution for drug response.'
The development of tailor-made pharmaceutics is especially useful in the field of oncology, since most anticancer agents have a very narrow therapeutic index. This sometimes leads to lack of any anti-tumor response or a high level of side effects. Heritable genetic variations (germline polymorphisms) in genes encoding for drug transporters, drug metabolizing enzymes or drug targets have been shown to influence the pharmacokinetics and pharmacodynamics of many drugs including drugs used in cancer therapy. There is a rapid development in the field of targeted anti-cancer agents, whereas the necessary accompanying pharmacogenetic research during drug development is lacking. It is important to conduct these studies for new anticancer agents to increase knowledge of variants in genes encoding for both drug metabolizing enzymes and drug targets, and to understand interindividual variability in pharmacokinetics and pharmacodynamics. Ultimately, this may lead to a better, tailor-made anticancer therapy with less side effects and more effective use of novel drugs in the future.

In **Chapter 5** the pharmacogenetics of telatinib (BAY 57-9352), a tyrosine kinase inhibitor of VEGFR-2, and VEGFR-3, used in patients with advanced or metastatic solid tumors is studied. **Chapter 10** describes the pharmacogenetic investigations of danusertib (PHA-739358), a small-molecule pan-aurora kinase inhibitor, used in similar patients.

A general discussion of the reported studies described in this thesis is presented in **Chapter 11**. Further, a summary of this thesis in both English and Dutch are provided.