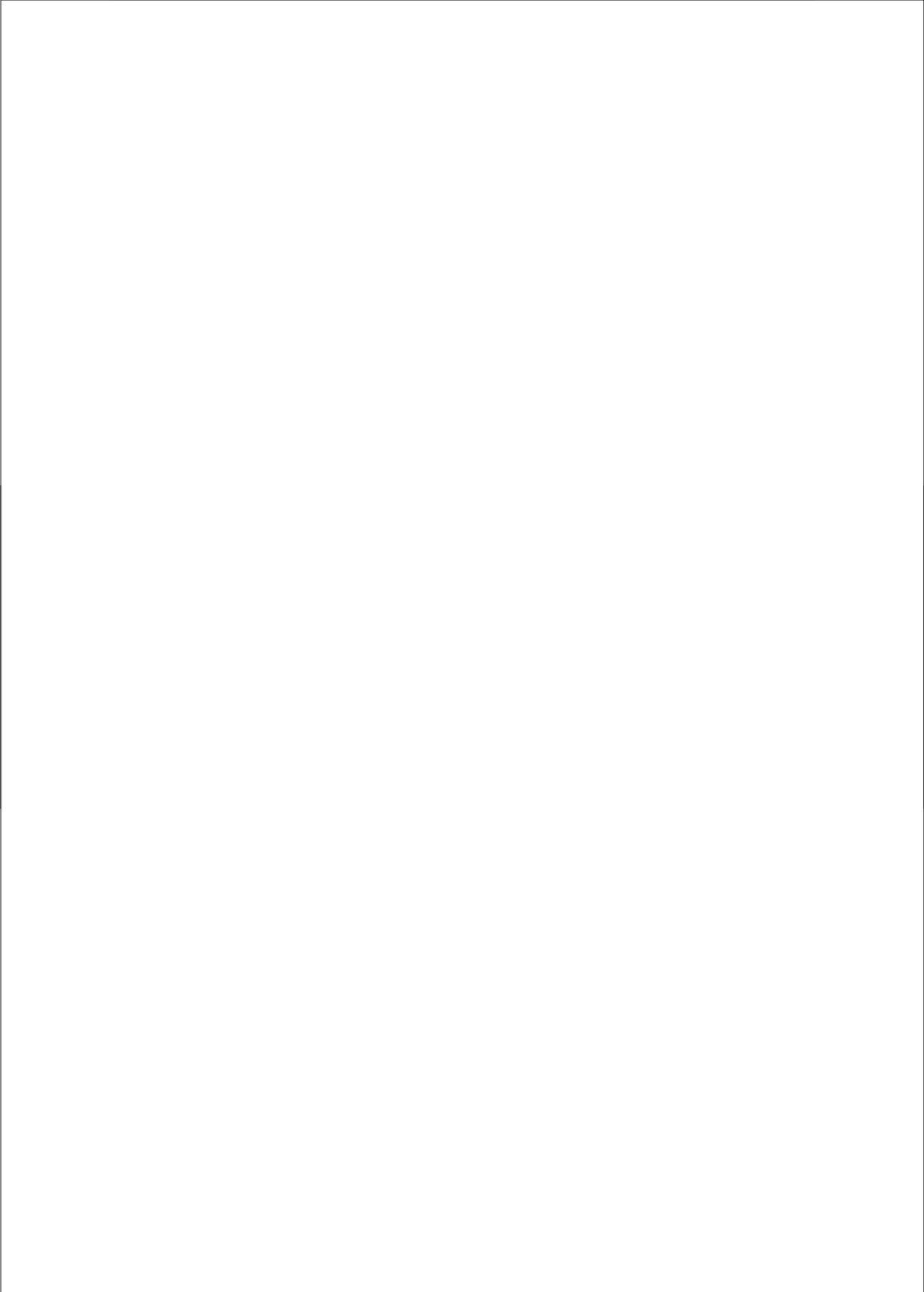# Chapter 14

## Summary

The development of targeted therapy has significantly improved the outcome of patients with metastatic renal cell cancer (mRCC). Among the approved targeted agents, sunitinib has achieved an important place in the treatment of this disease. In this thesis, several clinical and pharmacodynamic aspects regarding sunitinib treatment in mRCC patients are described. **Chapter 1** provided an introduction on the treatment of mRCC with a particular focus on sunitinib. Thereafter, the contents of this thesis are divided in three parts.

**Part I: Efficacy of sunitinib in renal cell cancer**
In **Chapter 2**, the efficacy of sunitinib in primary renal cell cancer (RCC) tumors in seventeen patients who presented with primary metastatic disease was described. Although primary tumors are usually refractory to cytokine-based therapy, sunitinib induced a significant reduction in tumor volume with concomitant development of extensive tumor necrosis. As the drug was capable of inducing an important tumor response in primary tumors, this might result in improved surgical resection.
In **Chapter 3A**, the clinical impact of neoadjuvant sunitinib was explored on surgical management of primary tumors with surgery-limiting features which included complex primaries and/or bulky locoregional metastases. Although six out of ten surgery-limiting tumor sites showed a reduction in tumor size, the extent of downsizing by neoadjuvant sunitinib was limited and cytoreductive surgery was reconsidered in only three patients. In addition, in **Chapter 3B** it was demonstrated that neoadjuvant sunitinib for resectable primary tumors can have a negative impact on surgical management. Two mRCC patients were described who developed a progressive caval vein thrombus during sunitinib treatment, consequently impeding the initially planned surgery.
Since localization of metastatic disease in the brain represents another RCC tumor location difficult to treat, the occurrence of brain metastases during sunitinib treatment was reported in **Chapter 4**. In a period of two years, nine out of 91 sunitinib-treated mRCC patients developed symptomatic brain metastases, which represented the first sign of progressive disease. Remarkably, six out of nine patients developed central nervous system (CNS) symptoms in the 2-week rest period. Lesions may have been masked by an anti-edema effect of sunitinib during the 4 weeks-on period of the treatment cycle. These findings suggest that sunitinib is inadequate for control of brain metastases and may temporarily suppress their existence. After radiotherapy or surgery for brain metastases, sunitinib could be safely continued and showed persisting efficacy in the extra-cerebral tumor sites. Therefore, new and isolated progression of RCC in CNS is no indication for permanent discontinuation of sunitinib.
In **Chapter 5**, it was examined whether genetic polymorphisms have predictive value for sunitinib efficacy in mRCC patients. To that end, a retrospective multicenter pharmaco-

genetic association study was performed in 136 clear cell mRCC patients treated with sunitinib. Thirty polymorphisms related to the pharmacokinetics and pharmacodynamics of the drug were investigated for a possible association with progression-free survival (PFS) and overall survival (OS). Apart from three clinical characteristics [Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria, number of metastatic sites and age], genetic polymorphisms in three genes involved in the pharmacokinetics of sunitinib (*CYP3A5*, *NR1I3* and *ABCB1*) were predictive factors for PFS. The results of this study warrant prospective validation and further clarification of the role of these genetic determinants in sunitinib exposure and efficacy.

**Part II: Side-effects of sunitinib**

In **Chapter 6**, the toxicity and efficacy of sunitinib were described in 82 mRCC patients included in a compassionate use programme. To this end, adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE). The observed efficacy of sunitinib was comparable with that reported in previous phase III trials. However, the observed toxicity seemed to be more severe, as almost half of the group of patients needed a dose reduction because of treatment-related side-effects. Most important toxicities requiring a lower dose included stomatitis, fatigue, hand-foot syndrome and a combination of grade 1-2 side-effects. Severe toxicity, defined as dose reduction or permanent discontinuation, was highly related to low body surface area, high age and female gender. On the basis of these patient characteristics, a model could be developed to predict the probability of severe toxicity in patients treated with sunitinib.

In **Chapter 7**, the occurrence of severe cognitive disorders induced by sunitinib was reported. Three elderly patients with mRCC developed cognitive and behavioral changes while on sunitinib which were reversible upon discontinuation. Brain metastases were excluded and the neurological symptoms disappeared after discontinuation of the drug. All three patients had preexisting arteriosclerotic leukoencephalopathy which most likely has contributed to the development of these cognitive side-effects. Therefore, physicians should be aware of cognitive disorders in elderly patients who are treated with sunitinib. In case such cognitive disorders develop, brain metastases should be excluded and sunitinib should temporarily be discontinued. As described earlier, sunitinib-induced side-effects can be severe. Hence, tools are warranted to predict the toxicity of sunitinib in individual patients in order to select patients for alternative dosing.

In **Chapter 8**, genetic polymorphisms in the pharmacokinetic and pharmacodynamic pathways of sunitinib were identified that predispose for the development of sunitinib-induced side-effects. In 219 patients treated with sunitinib, several genetic variants were associated with the development of leucopenia, mucosal inflammation, hand-foot syn-

drome and any toxicity higher than grade 2. The identified genetic polymorphisms encoded for metabolizing enzymes, efflux transporters, and drug targets of sunitinib. Development of leucopenia was associated with genetic polymorphisms in *CYP1A1* 2455A/G, *FLT3* 738T/C and the *NR1I3* haplotype. In addition, mucosal inflammation and hand-foot syndrome were associated with genetic polymorphisms in *CYP1A1* 2455A/G and the *ABCB1* haplotype, respectively. Any toxicity higher than grade 2 prevalence was increased when the T allele of vascular endothelial growth factor receptor (*VEGFR*)-*2* 1191C/T or a copy of TT in the *ABCG2* haplotype were present. Validation of the importance of specific genetic polymorphisms in the development of sunitinib-induced side-effects should be carried out in an independent patient population.

**Part III: Potential biomarkers**

In **Chapter 9**, new response criteria that incorporate the development of tumor necrosis were evaluated for early prediction of sunitinib efficacy. To that end, criteria defined by Choi et al were used in the evaluation of computed tomography (CT) scans in 55 sunitinib-treated mRCC patients. According to these criteria, a partial response (PR) was defined as a ≥ 10% decrease in size or a ≥ 15% decrease in attenuation. At first evaluation after a median period of 1.9 months, the Choi criteria were significantly better predictive for PFS and OS than the standard Response Evaluation Criteria In Solid Tumors (RECIST). However, the predictive value of the Choi criteria was similar to that of RECIST at later time points. Although the Choi criteria could be useful to early identify mRCC patients who benefit from sunitinib, these criteria were not able to early select patients without benefit from the drug. Therefore, the use of the Choi criteria will not change the management of sunitinib-treated mRCC patients.

In **Chapter 10**, the remarkable changes in hemoglobin levels during sunitinib treatment were reported. In 82 mRCC patients, a zig-zag pattern was observed in hemoglobin levels and erythrocyte numbers. During the 4 weeks-on treatment, a transient increase in hemoglobin and erythrocyte count occurred, which diminished rapidly during the 2-week rest period. Although the increase in erythrocyte numbers was accompanied by a rise in plasma erythropoietin, an erythropoietin-induced rise in erythrocytes is not expected to diminish rapidly within the 2 weeks of rest. On the basis of previous studies and our findings, it was hypothesized that the cyclic kinetics of hemoglobin and erythrocytes were not caused by an increase in erythropoiesis, but are likely the result of a temporary loss of intravascular fluid caused by inhibition of VEGFR-2 and subsequent reduction of nitric oxide.

In **Chapter 11**, the effects of sunitinib were measured on mature circulating endothelial cells (CEC) and hematopoietic progenitor cells (HPCs) in blood obtained from mRCC patients. Changes in circulating levels of CECs and HPCs may reflect sunitinib activity on

tumor neovasculature. In particular, the kinetics of specific populations of small VEGFR2-expressing CECs [CD45$^{neg}$)/CD34$^{bright}$)] and HPCs [CD45$^{dim}$)/CD34$^{bright}$)] were analyzed. These populations showed opposite kinetics; the CECs increased, whereas the HPCs decreased. This increase in CECs is likely the result of sunitinib activity in immature tumor vessels. In addition, an increased number of CECs after 14 days of sunitinib treatment was associated with a longer PFS when compared with patients with a decreased number of CECs.

To further investigate the effects of sunitinib on tumor endothelium, a study, reported in **Chapter 12**, was performed to measure changes in plasma proteins associated with activated tumor endothelium. To that end, plasma samples from sunitinib-treated mRCC patients were investigated for levels of the vascular endothelial growth factor (VEGF), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular cell adhesion molecule-1 (sICAM-1), von Willebrand factor (vWF), circulating angiopoietin-2 (Ang-2) and soluble Tie-2 (sTie-2). This study showed that tumor burden was positively associated with baseline circulating Ang-2. Sunitinib induced a decrease in circulating Ang-2 and sTie-2 levels, whereas levels of sVCAM-1 and VEGF significantly increased. The decrease in circulating Ang-2 was positively associated with the percentage decrease in tumor burden after sunitinib treatment. Hence, the decline in circulating Ang-2 may represent a biomarker of sunitinib activity in RCC tumors.

Finally, in **Chapter 13** the effects of sunitinib on the systemic vasculature were reported. Sunitinib treatment is associated with systemic hypertension, which may be caused by the development of functional rarefaction (a decrease in perfused microvessels) or structural rarefaction (a reduction in anatomic capillary density). In **Chapter 13A**, it was investigated whether sunitinib treatment leads to impairment of microvascular function and/or reduction of capillary density in the dorsal skin of the finger. In mRCC patients, sunitinib induced a rise in systolic and diastolic blood pressure, whereas the capillary density in the skin decreased. This decrease was associated with an increase in systolic and diastolic blood pressure. In **Chapter 13B**, it was demonstrated that these effects were reversible after discontinuation of sunitinib. Patients with a greater reduction in capillary density had a prolonged PFS. Therefore, reduction in skin capillary density might be a predictive marker of clinical outcome in sunitinib-treated mRCC patients.