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## Molecular imaging to guide clinical decisions on targeted treatment of solid tumors

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# **Chapter 8**

## **Summary**

Over the last decade, targeted therapies have rapidly emerged in oncology, fuelled by increasing knowledge of inter- and intracellular signaling pathways. Small molecules and antibodies that inhibit essential targets within signaling pathways can induce tumor responses in subsets of cancer patients. A major challenge is the selection of patients who will most likely benefit from a targeted treatment approach. The aim of this thesis is to investigate the role of molecular PET imaging as biomarker to guide clinical decisions on targeted treatment of solid tumors, with an emphasis on GIST and highly vascular tumor types.

In **chapter 2**, an overview is presented of progress in biomarker development in solid cancer. Whereas prognostic biomarkers provide information about outcome regardless of treatment, predictive biomarkers give information about the effect of therapeutic interventions. A biomarker can be prognostic as well as predictive, and a predictive biomarker can be a treatment target. Expression or mutation of several genes, that all seem key regulators of disease initiation and progression, have proven to be relevant prognostic and/or predictive biomarkers such as estrogen receptor and progesterone receptor expression and human epidermal growth factor receptor 2 overexpression in breast cancer, Philadelphia chromosome in chronic myeloid leukemia, c-KIT mutations in GIST and epidermal growth factor receptor 1 mutations in non-small cell lung cancer. Identification and validation of novel predictive biomarkers progresses rather slowly because in most tumors a series of alterations rather than a single mutation is responsible for tumor behavior. A grading system and guidelines for reporting of biomarker studies have been developed. Future perspectives for the development of prognostic and predictive markers are discussed.

GISTs are characterized by activating mutations in tyrosine kinase receptors c-KIT or platelet derived growth factor receptor alpha. The tyrosine kinase inhibitor imatinib blocks these receptors and effectively inhibits tumor growth in the majority of the patients. However, about 15% of the patients have primary imatinib resistant disease, defined as progressive disease at first computed tomography (CT) evaluation. In **chapter 3** we investigated in 36 consecutive metastatic or locally advanced GIST patients whether early change in tumor  $^{18}\text{F}$ -FDG uptake predicts primary imatinib resistance. Patients underwent  $^{18}\text{F}$ -FDG PET scans before and 1 week after start of imatinib. The relationship between early  $^{18}\text{F}$ -FDG PET response (according to the European Organisation for Research and Treatment of Cancer guideline) and CT response after 2 months of treatment (according to the response evaluation criteria in solid tumors (RECIST) version 1.0 and the Choi criteria) was investigated. In the 30 evaluable patients for  $^{18}\text{F}$ -FDG PET response mean of tumor maximum standardized uptake values (mean SUVmax) decreased from 7.4 (standard deviation (SD) 3.8, range 2.2-18.4) to 3.0 (SD 2.1, range 0.1-11.8) after 1 week imatinib treatment ( $P < 0.001$ ). Twenty-six patients had metabolic response and 4 had metabolic stable disease.  $^{18}\text{F}$ -FDG PET response had a high positive predictive value for clinical benefit (combination of complete response, partial response and stable disease) according to RECIST: 92% (95% confidence interval (CI) 75-99%) and the Choi criteria: 95% (95% CI 76-100%). However, the false negative rate was respectively 11% (95% CI 2-30%) and 9% (95%

CI 1-30%). As the upfront chance of clinical benefit is 85%, no predictive information on treatment outcome is added by early assessing metabolic response. In conclusion, although  $^{18}\text{F}$ -FDG PET response has a high positive predictive value for clinical benefit from imatinib in GIST patients, it cannot be used to predict primary resistance. Imatinib is an extremely effective agent for this disease and should, in the advanced setting, be continued until convincing clinical and/or radiological evidence of progressive disease or unacceptable toxicity.

In **chapter 4** we investigated the ability of the novel VEGF-PET tracer  $^{89}\text{Zr}$ -ranibizumab to visualize dynamic angiogenic changes in tumors in mouse xenograft models of human cancer following treatment with the tyrosine kinase inhibitor sunitinib. Ranibizumab is a monoclonal antibody fragment derivative of bevacizumab. It has a higher affinity for all soluble and matrix bound human VEGF-A isoforms than bevacizumab and it allows fast and sequential follow up PET scans, as its serum half-life is only 2 to 6 hours in mice. The effect of treatment and withdrawal of sunitinib on metabolism and perfusions was investigated simultaneously with  $^{18}\text{F}$ -FDG PET, and  $^{15}\text{O}$ -water PET, and imaging results were compared with tumor growth, plasma VEGF levels and immunohistologic analyzes. In contrast to  $^{18}\text{F}$ -FDG and  $^{15}\text{O}$ -water PET,  $^{89}\text{Zr}$ -ranibizumab PET demonstrated dynamic changes during sunitinib treatment within the tumor with a strong decline in signal in the tumor center and only minimal reduction in tumor rim, with a pronounced rebound after sunitinib discontinuation.  $^{89}\text{Zr}$ -ranibizumab PET results corresponded with tumor growth and immunohistochemical vascular- and tumor- markers. In conclusion,  $^{89}\text{Zr}$ -ranibizumab-PET allows noninvasive dynamic and spatial *in vivo* visualization and quantification of VEGF signaling.

In **chapters 5-7** we took this approach to the clinic and explored in small feasibility studies the potential of  $^{89}\text{Zr}$ -bevacizumab PET as a prognostic biomarker (in VHL patients) and as predictive biomarker of targeted therapy (in renal cell carcinoma and neuroendocrine tumor patients).

Patients with VHL disease are at risk to develop benign and malignant vascular tumors. Local VEGF-A production is supposed to play an important role in development of disease manifestations. In **chapter 5** we aimed to assess in 22 adult VHL patients with at least 1 measurable hemangioblastoma, whether VHL-associated lesions can be visualized with  $^{89}\text{Zr}$ -bevacizumab PET. Secondary objective was to explore whether  $^{89}\text{Zr}$ -bevacizumab PET can differentiate progressive lesions from non-progressive lesions. 37 MBq  $^{89}\text{Zr}$ -bevacizumab was injected 4 days before the PET scan. PET scans were fused with routine magnetic resonance imaging (MRI) of the central nervous system and abdominal MRI or CT. SUVmax was calculated for disease manifestations visible on PET and for normal organs. Progressive lesions were defined as new lesions, lesions that became symptomatic and lesions  $\geq 10$  mm that increased  $\geq 10\%$  and  $\geq 4$  mm on repeat anatomic imaging within one year.

$^{89}\text{Zr}$ -bevacizumab PET visualized 59 VHL manifestations, 0-17 per patient, with a median SUVmax of 8.5 (range 1.3 – 35.8). Detection rate for lesions  $\geq 10$  mm was 30.8%. Seven additional hotspots without substrate on baseline anatomic imaging were found, 2 were also detected on anatomic imaging during follow-up. Nine out of 25 progressive lesions

were visible on PET (SUVmax 0.9-8.9). Detection rate nor SUVmax was different for progressive versus non-progressive lesions. Two patients started treatment with bevacizumab plus interferon- $\alpha$ . One patient with intense hemangioblastoma tracer uptake had ongoing benefit after 27 months of bevacizumab treatment whereas a patient with low uptake in renal cell carcinoma died within 2 months of progression of metastatic renal cell carcinoma. Concluding, VHL lesions can be visualized with  $^{89}\text{Zr}$ -bevacizumab PET with a striking heterogeneity in tracer accumulation.  $^{89}\text{Zr}$ -bevacizumab uptake did not predict progression within 12 months but might be useful to select patients for bevacizumab treatment.

In **chapter 5A** we describe the effect of bevacizumab in a 55-year-old man with hereditary hemorrhagic telangiectasia with intractable pain and frequent episodes of pancreatitis related to pancreatic arteriovenous malformations. An  $^{111}\text{In}$ -bevacizumab single photon emission computed tomography (SPECT) showed elevated tracer uptake in the arteriovenous malformations. Bevacizumab treatment was started at a dose of 5.0 mg per kilogram of body weight every 2 weeks. Epistaxis stopped immediately, the skin vascular signs became less pronounced, and the frequency and severity of pancreatitis diminished. After 5 months, the dose was increased to 7.5 mg per kilogram every 2 weeks. Thereafter, morphine and tube feeding could be discontinued, and the patient resumed work. No change in the volume of the arteriovenous malformations was observed on CT. After 1 year, the patient was still receiving bevacizumab treatment with ongoing benefit regarding pancreatitis frequency and severity.

In **chapter 6** we investigated in metastatic renal cell carcinoma patients tumor uptake of  $^{89}\text{Zr}$ -bevacizumab, before and during anti-angiogenic treatment as a potential predictive marker for treatment efficacy. Patients underwent  $^{89}\text{Zr}$ -bevacizumab PET scans at baseline and 2 and 6 weeks. Treatment consisted of bevacizumab 10 mg/kg every 2 weeks with interferon- $\alpha$  3 to 9 million units 3 times per week, or sunitinib 50 mg daily, for 4 out of every 6 weeks. Tumor uptake was compared to plasma VEGF-A and time to disease progression.  $^{89}\text{Zr}$ -bevacizumab PET visualized 125 tumor lesions in 22 patients. Median SUVmax was 6.9 (range 2.3 – 46.9), varying from 3.8 (range 2.7 – 15.4) to 36.3 (range 25.7 – 46.9) between patients. Bevacizumab/interferon- $\alpha$  treatment ( $n = 11$ ) decreased SUVmax 47.0% ( $P < 0.0001$ ) at 2 weeks and an additional 9.7% ( $P = 0.015$ ) at 6 weeks. Sunitinib ( $n = 11$ ) decreased SUVmax by 14.3% at 2 weeks ( $P = 0.006$ ), but at 6 weeks SUVmax was 72.6% ( $P < 0.0001$ ) above baseline. SUVmax was not related to plasma VEGF-A at baseline, 2 weeks and 6 weeks. Baseline mean tumor SUVmax  $> 10.0$  in the three most intense lesions corresponded with longer time to disease progression (89.7 versus 23.0 weeks, hazard ratio 0.22, 95% CI 0.05 – 1.00). In conclusion, high  $^{89}\text{Zr}$ -bevacizumab tumor uptake was demonstrated in renal cell carcinoma patients with remarkable inter- and intra-patient heterogeneity. Treatment with bevacizumab/interferon- $\alpha$  strongly decreased tumor uptake whereas sunitinib treatment induced a modest reduction with an overshoot after 2 drug-free weeks. High baseline tumor SUVmax was associated with longer time to disease progression.

The oral mTOR inhibitor everolimus increases progression free survival in patients with advanced neuroendocrine tumors. Currently, no biomarkers are available to select patients who will benefit from everolimus. Everolimus can reduce VEGF-A production by tumor cells.  $^{89}\text{Zr}$ -bevacizumab PET might therefore be able to serve as an early read out of treatment efficacy. In **chapter 7**, we aimed to investigate the effect of everolimus treatment on tumor uptake of  $^{89}\text{Zr}$ -bevacizumab in patients with advanced well differentiated neuroendocrine tumors.  $^{89}\text{Zr}$ -bevacizumab PET scans were performed before, and during everolimus treatment at 2 and 12 weeks.  $^{89}\text{Zr}$ -bevacizumab uptake was quantified by SUVmax. Tumor response according to RECIST 1.1 and the percentage of change in the sum of target lesion diameters was determined on CT every 3 months. In four out of 14 patients that were entered in the study, no tumor lesions were visualized with  $^{89}\text{Zr}$ -bevacizumab PET. In the remaining patients, 19% of tumor lesions  $\geq 1$  cm on the baseline routine CT scan were visualized. Median tumor SUVmax decreased during everolimus treatment with 7% at 2 weeks ( $P = 0.09$ ) and 35% at 12 weeks ( $P < 0.001$ ). Delta SUVmax at 2 and 12 weeks correlated with the percentage change in the sum of target lesion diameters on CT at 6 months ( $r^2 = 0.51$ ,  $P < 0.05$ ,  $r^2 = 0.61$ ,  $P < 0.01$ , respectively). In conclusion, this study demonstrates variable  $^{89}\text{Zr}$ -bevacizumab tumor uptake in patients with advanced neuroendocrine tumors at baseline, and a decrease of  $^{89}\text{Zr}$ -bevacizumab tumor uptake during everolimus treatment.

