Chapter 9

Summary

Positron emission tomography (PET) is an imaging technique that may be useful for individualized treatment planning in cancer patients. For that purpose, radiolabeling anticancer drugs with positron emitters is promising, as these may then be used to monitor drug pharmacokinetics and pharmacodynamics in patients non-invasively. In this thesis, validation and clinical implementation of a newly radiolabeled anticancer drug, carbon-11 labeled docetaxel ($[^{11}C]$docetaxel), in patients with lung cancer were presented.

In **Chapter 1**, principles of PET and applications of several PET tracers in oncology were introduced. In addition, development of the novel PET tracer $[^{11}C]$docetaxel and its validation in lung cancer patients was described.

In **Chapter 2**, the role of PET and radiolabeled anticancer drugs in predicting tumor resistance was reviewed. In this chapter, the focus was on resistance pathways that may impede drug delivery to tumors and how PET can help to reveal these pathways. Mechanisms of drug resistance that were discussed included factors that may affect distribution of drugs within the body, bioavailability of drugs in the circulation, as well as transport of drugs to tumors. Within that framework, radiolabeled anticancer drugs that have been developed, together with their stage of clinical implementation, were reviewed. It was concluded that use of radiolabeled anticancer drugs (e.g. $[^{18}F]$paclitaxel and $[^{18}F]$fluorouracil) provides a unique means for personalized treatment planning and drug development. In this chapter, it was also argued that combining these specific PET tracers with other less specific ones, such as tracers for blood flow (e.g. $[^{15}O]H_2O$) and efflux transporters (e.g. $[^{11}C]$verapamil), may provide additional information on drug resistance mechanisms. Finally, it was mentioned that radiolabeled anticancer agents may be valuable for evaluating optimal timing of combination therapies.

As tumor perfusion may influence the delivery of radiolabeled drugs to tumors, the validity and reproducibility of dynamic $[^{15}O]H_2O$ PET/CT scans for measuring tumor perfusion were assessed in **Chapter 3**. In addition, quantitative accuracy of parametric perfusion images was validated. To that end, eleven patients with non–small cell lung cancer (NSCLC) underwent two dynamic $[^{15}O]H_2O$ PET scans on the same day. This validation study showed that the use of image derived input functions (IDIFs) obtained from the ascending aorta was an accurate alternative for arterial blood sampling when quantifying tumor perfusion. In addition, it was shown that image quality obtained with a clinical PET/CT scanner enabled generation of accurate parametric perfusion images. Volumes of interest (VOIs) delineated on low-dose computed tomography (LD-CT) scans had the highest reproducibility and changes of more than 16% in tumor perfusion were likely to represent treatment effects.

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Chapters 4 to 7 described a series of steps that were followed in order to validate the use of [^{11}C]docetaxel in clinical PET studies.

In **Chapter 4**, the biodistribution of [^{11}C]docetaxel was determined in healthy male rats at 5, 15, 30 and 60 minutes after injection. This preclinical study showed the highest [^{11}C]docetaxel uptake in spleen, followed by urine, lungs and liver, whereas brain and testes showed the lowest uptake. Within less than 5 minutes, [^{11}C]docetaxel essentially had cleared from blood and plasma. This preclinical study was needed to obtain an initial estimate of the expected radiation dose in humans, which in turn was required for obtaining ethics permission to conduct human studies.

In **Chapter 5**, biodistribution and actual human radiation dosimetry of [^{11}C]docetaxel were determined in seven patients with solid tumors using whole body PET/CT scans. Gall bladder and liver showed high [^{11}C]docetaxel uptake, whilst uptake in brain and normal lung was low. In the liver, the percentage injected dose at 1 hour was 47 ± 9%. [^{11}C]docetaxel was rapidly cleared from plasma and no radiolabeled metabolites were detected. [^{11}C]docetaxel uptake in tumors was moderate and highly variable between tumors. The effective dose of [^{11}C]docetaxel was 4.7 µSv·MBq^{-1}. In contrast to the previous study in rats, [^{11}C]docetaxel showed low uptake in human lungs. Therefore, it was concluded that [^{11}C]docetaxel may be a promising tracer for tumors in the thoracic region.

In **Chapter 6**, the feasibility of quantitative [^{11}C]docetaxel scans in lung cancer patients was evaluated. In addition, it was investigated whether [^{11}C]docetaxel kinetics were associated with tumor perfusion, tumor size, or dexamethasone administration. In this study, 34 lung cancer patients underwent dynamic PET-CT using [^{11}C]docetaxel and [^{15}O]H$_2$O. The first 24 patients were premedicated with dexamethasone. For quantification of [^{11}C]docetaxel kinetics, the optimal tracer kinetic model was developed. Tumor kinetics of [^{11}C]docetaxel were irreversible and could be quantified using the Patlak method. Furthermore, it was shown that reproducible quantification of [^{11}C]docetaxel kinetics in tumors was possible using an IDIF. In tumors, the net rate of influx (K_i) of [^{11}C]docetaxel was variable and strongly related to tumor perfusion, but not to tumor size. In addition, patients pre-treated with dexamethasone, a potent inducer of the efflux transporter ABCB1, showed lower [^{11}C]docetaxel uptake in tumors. In a subgroup of patients who subsequently received docetaxel therapy, relative high [^{11}C]docetaxel uptake was related with improved tumor response. Accordingly, it was concluded that quantification of [^{11}C]docetaxel kinetics in lung cancer was feasible in a clinical setting and that the observed variation in [^{11}C]docetaxel kinetics between tumors may reflect differential sensitivity to docetaxel therapy.

As pharmacokinetics of [^{11}C]docetaxel at tracer doses may be different from those at therapeutic doses, the microdosing concept was validated for [^{11}C]docetaxel in **Chapter**

7. The research question to be addressed was whether a PET study using a tracer dose of [11C]docetaxel could predict tumor uptake of unlabeled (cold) docetaxel during a therapeutic infusion. For this purpose, docetaxel-naïve lung cancer patients underwent two [11C]docetaxel PET scans, one after a bolus injection of a tracer dose [11C]docetaxel and another during a combined infusion of a tracer dose [11C]docetaxel and a therapeutic dose of docetaxel (75 mg·m^{-2}). Compartmental and spectral analyses were used to quantify [11C]docetaxel tumor kinetics. In addition, [11C]docetaxel PET measurements were used to estimate the area under the curve (AUC_{Tumor}) of cold docetaxel in tumors. [11C]docetaxel K_i in tumors was comparable during microdosing and therapeutic scans. [11C]docetaxel AUC_{Tumor} during the therapeutic scan could be predicted reliably using an impulse response function derived from the microdosing scan together with the plasma curve of [11C]docetaxel during the therapeutic scan. At 90 minutes, the accumulated amount of cold docetaxel in tumors was < 1% of the total infused dose of docetaxel. [11C]docetaxel K_i derived from the microdosing scan correlated with AUC_{Tumor} of cold docetaxel during the therapeutic scan and with tumor response to docetaxel therapy. Based on these results, it was concluded that microdosing data of [11C]docetaxel PET can indeed be used to predict tumor uptake of cold docetaxel during chemotherapy. The study in this chapter provides a framework for investigating the PET microdosing concept for radiolabeled anticancer drugs in patients.

In **Chapter 8**, the effects of the anti-angiogenic drug bevacizumab on tumor perfusion and [11C]docetaxel uptake in non-small cell lung cancer (NSCLC) was investigated. Bevacizumab is a humanized monoclonal antibody that targets circulating vascular endothelial growth factor (VEGF) and subsequently prevents binding of VEGF to its receptors. It is assumed that anti-angiogenic drugs, such as bevacizumab, transiently normalize the abnormal tumor vasculature and contribute to improved delivery of subsequent chemotherapy. To investigate this concept, a study was performed in NSCLC patients using PET and [11C]docetaxel. In NSCLC, bevacizumab reduced both perfusion and [11C]docetaxel K_i within 5 hours. These effects persisted after 4 days and were not associated with significant changes in tumor heterogeneity of [11C]docetaxel uptake. Reduction in [11C]docetaxel delivery to tumors was accompanied by rapid reduction in circulating levels of VEGF, but not with changes in cardiovascular parameters such as blood pressure, cardiac output and capillary density in the skin. The clinical relevance of these findings is notable, as there was no evidence for substantial improvement in drug delivery to tumors after administration of bevacizumab. This study highlights the importance of drug scheduling and advocates further studies to optimize scheduling of anti-angiogenic drugs.