Introduction
Chapter 1

Lean back and read. Louisiana, USA 2000.
Introduction

Background
Pyrimidine antagonists belong to the group of antimetabolite anti-cancer drugs and show structural resemblance with naturally occurring nucleotides. Their action is accomplished through incorporation as false precursor in DNA or RNA or through inhibition of proteins involved in nucleotide metabolism. The most commonly used pyrimidine antagonists are 5-fluorouracil, gemcitabine and cytarabine. Newer oral variants of 5-fluorouracil are capecitabine and tegafur. 5-Fluorouracil and its analogues are used e.g. in the treatment of colorectal-, breast- and head and neck cancer [1-3], whereas gemcitabine is especially prescribed for non-small cell lung cancer and pancreatic cancer [4,5]. Cytarabine is administered in the treatment of leukaemia [6]. All pyrimidine antagonists are prodrugs and intracellular conversion into cytotoxic nucleosides and nucleotides is needed to produce cytotoxic metabolites. Proteins, involved in pyrimidine metabolism handle these synthetic drugs, as if they were naturally occurring substrates. The extensive metabolism of pyrimidine antagonists implies that the intracellular concentrations of cytotoxic metabolites, largely depend on intracellular metabolic enzyme activity. Therefore, understanding of the genetics and kinetics of the range of (iso)enzymes involved in pyrimidine antagonist metabolism is essential for the optimal utilization of these anticancer drugs. Dihydropyrimidine dehydrogenase is the enzyme that is responsible for the catabolism of 5-fluorouracil and its analogues [7]. Gemcitabine and cytarabine are predominantly metabolized by cytidine deaminase [8]. Thus, not only body surface area, but particularly the total capacity of metabolizing enzymes in an individual, in combination with some other factors such as organ function, food and drug interactions, age and gender, determine the clearance of these drugs.

Aim of the thesis
This thesis aims to clarify the role of a number of potential factors in the clinical pharmacology and pharmacogenetics of pyrimidine antagonists, related to the occurrence of side effects, in order to improve the drug safety of pyrimidine antagonist chemotherapy.

Outline of the thesis
In chapter 2, the enzymology and genetics of the proteins, involved in the metabolism and action mechanism of pyrimidine antagonists are discussed. This should serve as a basis for adequate understanding of factors involved in the clinical pharmacology of these drugs. Section A, comprising chapters 3, 4.1, 4.2, and 5, focuses on a number of clinical pharmacological and pharmacogenetic aspects of 5-fluorouracil chemotherapy. Chapter 3 describes a novel assay for quantification of 5-fluorouracil in plasma, to be used for studying 5-fluorouracil pharmacokinetics. 5-Fluorouracil clearance is mainly determined
by dihydropyrimidine dehydrogenase activity, which is highest in the liver. Therefore, *chapter 4.1* focuses on the impact of liver metastases on 5-fluorouracil pharmacokinetics, whereas *chapter 4.2* describes the impact of dihydropyrimidine dehydrogenase deficiency caused by a polymorphism in the dihydropyrimidine dehydrogenase gene on 5-fluorouracil clearance. Since early detection of dihydropyrimidine dehydrogenase deficiency may prevent extreme 5-fluorouracil treatment related toxicity, *chapter 5* explores the use of an oral uracil challenge for dihydropyrimidine phenotyping.

In section B, comprising *chapters 6, 7, 8 and 9* a number of clinical pharmacological and pharmacogenetic aspects of gemcitabine chemotherapy are evaluated. Gemcitabine has been recognized as a potent radiosensitizer, and as such, an interesting candidate for pre-radiotherapy radiosensitization in non-small cell lung cancer [9]. The mechanism of gemcitabine mediated radiosensitization is yet poorly understood. Inhibition of DNA double strand break repair by non-homologous end-joining was previously excluded as a means of radiosensitization [9]. In **Chapter 6** the role of *base excision repair* and *homologous recombination* with respect to gemcitabine induced radiosensitization is explored in cell line experiments.

**Chapter 7** describes a novel assay for determination of epirubicin in plasma and saliva. The excretion of cytotoxic drugs in saliva may be related to the development of side effects such as oral mucositis and diarrhea. Therefore, **chapter 8** focuses on the excretion of gemcitabine and epirubicin in saliva. In **chapter 9**, the potential interaction of gemcitabine and epirubicin at the level of plasma pharmacokinetics is explored. Additionally, the possible influence of a common genetic polymorphism in the cytidine deaminase gene on gemcitabine clearance is evaluated.

Finally, the **summary, general discussion and future perspectives** chapters summarize the main findings, strengths and limitations of the studies in the preceding chapters and give ideas for future research.
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References
