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The cytotoxic drug cyclo-pentenyl cytosine: from manufacturing to anti-tumor activity and (cardio)toxicity

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CHAPTER 1

AIM AND OUTLINE OF THE THESIS

The cytotoxic drug cyclopentenyl cytosine:
From manufacturing to anti-tumor activity
and *cardiotoxicity*

SCOPE OF THE THESIS

The aim of this study is to explore pharmaceutical aspects as well as anti-tumor activity and cardiotoxicity of the cytostatic drug cyclopentenyl cytosine.

OUTLINE

The experimental cytotoxic drug cyclopentenyl cytosine (CPEC) is a pyrimidine analogue of cytidine. After transmembrane transport, CPEC is subsequently phosphorylated by the enzymes uridine/cytidine kinase, nucleoside monophosphate-kinase (NMP-kinase) and nucleoside diphosphate-kinase (NDP-kinase) to form CPEC-triphosphate (CPEC-TP), being the major metabolite [1]. CPEC-TP is an inhibitor of cytidine triphosphate synthetase (CTP-synthetase), this enzyme catalyses the synthesis of the ribonucleotide cytidine triphosphate (CTP) [2,3]. Inhibition results in a decrease of RNA and DNA synthesis and S-phase accumulation. Moreover, a high CTP synthetase activity has been found in various malignant and non-malignant tissues in humans and animals [4,5], making this enzyme an attractive target for inhibition. Originally selected for its antiviral activity, most research has been done to investigate the activity of CPEC in several malignancies. In chapter 2 an overview of both the preclinical and early clinical studies with CPEC is given. These studies showed promising results on hematological malignancies and plans for phase I and II clinical trials were initiated.

As only the raw drug substance was available we developed a pharmaceutical formulation of the drug to be used in these clinical trials. A stable sterile infusion concentrate of CPEC was manufactured (chapter 3).

During an early phase I trial with CPEC in solid tumors, serious cardiotoxic side effects were observed [6]. As these side effects seemed to be dose related, future trials would start with low dose CPEC and plasma monitoring of CPEC levels would become necessary. Therefore, we developed a sensitive and rapid HPLC MS/MS method for measuring plasma levels of CPEC and its metabolite cyclopentenyl uridine (CPEU) (chapter 4).

To explore the antitumor potential of CPEC in leukemia, we tested the drug in an *in vivo* animal model for human ALL using NOD/scid (nonobese diabetic/severe combined immunodeficient) mice (chapter 5).

Before initiating clinical trials with the experimental drug, it was necessary to further study and understand the mechanism of the aforementioned cardiotoxic side effects of CPEC. Cardiotoxicity is not uncommon among cytotoxic agents and especially the anthracyclines are well known to cause severe cardiotoxicity. In chapter 6 the cardiotoxicity of several cytotoxic drugs is described including (possible) mechanisms and preventive measures.

The exploration of the cardiotoxic effects of CPEC and the underlying mechanism was studied in both *in vitro* and *in vivo* in animal models (chapter 7).

We further hypothesized that cardiotoxicity of cytotoxic drugs including CPEC, might have a genetic origin. We first performed a retrospective case control analysis in oncology patients having received the anthracycline doxorubicine. We investigated the differences in polymorphisms in several candidate genes between patients with and without anthracycline-induced cardiotoxicity and between cases and healthy control subjects. Furthermore, we tested *in vitro* in a rat cardiomyocyte cell line, whether doxorubicine and CPEC influenced the expression of genes that were suspected to be related with drug induced cardiotoxicity (chapter 8).

In chapter 9 the results of the studies presented in this thesis are interpreted and suggestions for further research are given. Chapter 10 provides a summary of the results.

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