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Introduction, aim and outline of this thesis
Cancer, the leading cause of death in many developed countries, is responsible for almost one third of all deaths worldwide. Every year almost 0.5% of the world population is diagnosed with cancer.¹ It is expected that cancer is set to become a major cause of morbidity and mortality in the next few decades in every region of the world, irrespective of level of resource. Recently Bray et al. predicted an increase in the incidence of all cancer cases from 12.7 million new cases in 2008 to 22.2 million by 2030.²

Nowadays many different treatment options for cancer are known: local therapies including surgery and radiotherapy and systemic therapy including chemotherapy, hormonal therapy, immunotherapy and targeted therapy. Unfortunately, many current anticancer drugs have non-ideal pharmaceutical and pharmacological properties, which can lead to adverse consequences, including suboptimal therapeutic activity, dose-limiting side effects and poor patient quality of life. Novel formulations of anticancer drugs are necessary to overcome these problems. The general aim and scope of this thesis is to explore several novel formulations and new classes of anticancer drugs in solid tumors.

**NOVEL FORMULATIONS**

The first part of this thesis focuses on two novel formulations, namely liposomal drug formulations and camptothecin glycoconjugate BAY 56-3722 (formerly BAY 38-3441).

**Liposomal drug formulations**

In Chapter 2, as a prelude to the next chapters, the liposomal anticancer drugs that are available in the clinic are reviewed. Liposomes are simple, self-assembling systems that consist of a bilayer membrane surrounding an aqueous interior compartment. They are generally formed from naturally occurring phospholipids and cholesterol.³ Considerable flexibility is possible in the design of liposomes with regard to, for example, their composition, size and drug release characteristics. Liposomal nanoparticles are designed to be multifunctional, with different components providing control over such properties as elimination half lives, permeability, biodistribution and targeting specificity.⁴ At present, several liposomal anticancer drugs are available in the clinic or are in advanced stages of clinical development. Approved drugs include pegylated liposomal doxorubicin (Doxil®/Caelyx®), nonpegylated liposomal doxorubicin (Myocet®), liposomal daunorubicin (DaunoXome®) and liposomal cytarabine (DepoCyte®). Although almost all studies show that liposomal formulations of anticancer drugs are less toxic than the non-encapsulated
formulations, some liposome-specific adverse effects such as various skin reactions, and also hypersensitivity reactions, were reported.

In Chapter 3, a dose-escalating phase I study of LiPlaCis, a liposomal formulated platinum compound, in patients with advanced solid tumors is reported. In Chapter 4 we describe a randomized two-period crossover, clinical bioequivalence study comparing the pharmacokinetics and safety of liposome-entrapped paclitaxel easy-to-use (LEP-ETU) formulation versus paclitaxel in Cremophor® EL (Taxol®) in patients with advanced cancer.

BAY 56-3722

In Chapter 5, we report the fate of BAY 56-3722 (formerly BAY 38-3441), a camptothecin glycoconjugate and the unique situation of a clinical hold after enrollment of 25 patients during a phase II study. This phase II study evaluates the antitumor activity of BAY 56-3722 in patients with recurrent or metastatic inoperable colorectal cancer (CRC) resistant to irinotecan.

NEW CLASSES OF ANTI CANCER DRUGS

Besides novel formulations, also new classes of anticancer drugs for solid tumors such as histone deacetylase (HDAC) inhibitors and cardiac glycosides could be useful in the treatment of cancer. The second part of this thesis focuses on HDAC inhibitors and cardiac glycosides.

HDAC inhibitors

The histone deacetylase inhibitors are a group of targeted agents which are characterized as class I-specific or as pan-deacetylase (pan-DAC) inhibitors, which show activity against both classes I and II HDACs. A lot of research was focused on the treatment of hematological malignancies, but in the last decade also clinical trials with HDAC inhibitors in solid tumors were conducted. In Chapter 6, as a prelude to the next chapter, the clinical trials in solid tumors of HDAC inhibitors are reviewed. We demonstrate that despite promising results in the treatment of hematological malignancies, HDAC inhibitors have generally not been effective in clinical trials involving solid tumors.

Chapter 7 describes a phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and various degrees of hepatic function.
Cardiac glycosides

Cardiac glycosides have a long history in the treatment of cardiac disease. However, several preclinical studies and also two phase I studies have shown that cardenolides may also have anticancer effects. The mechanisms of the anticancer effects of cardenolides may include intracellular decrease of $K^+$ and increase of $Na^+$ and $Ca^{2+}$; intracellular acidification; inhibition of IL-8 production and the TNF-α/NF-κB pathway; inhibition of DNA topoisomerase II and activation of the Src kinase pathway. In Chapter 8 we give an overview of these possible mechanisms and discuss their early development in cancer therapeutics. In Chapter 9 we summarize the preclinical data and the preliminary results of a prematurely stopped clinical phase I trial with UNBS1450, a semisynthetic cardenolide glycoside derivative. This drug is considered a promising anticancer agent targeting overexpressed sodium pump α subunits in malignant tumors.

An English and Dutch summary of this thesis, including future perspectives, is presented in Chapter 10.

REFERENCES


