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Summary and future perspectives
In this chapter the reported studies and reviews presented in this thesis are summarized. The first part of this thesis focuses on some novel formulations, especially camptothecin glycoconjugate BAY 56-3722 (formerly BAY 38-3441) and liposomal drug formulations. The second part of this thesis focuses on histone deacetylase (HDAC) inhibitors and cardiac glycosides, especially UNBS1450. Chapter 1 gives a general introduction and describes the general aim of this thesis to explore some novel formulations and new classes of anticancer drugs in solid tumors. It also describes the outline of the thesis.

NOVEL FORMULATIONS

Liposomal drug formulations

In Chapter 2, a review of liposomal anticancer drugs is presented. The main advantages, 1) improved pharmacokinetics and drug release; 2) enhanced cellular penetration; 3) tumor targeting and 4) multi-ingredients systems, and an up-to-date overview of the current clinical development are discussed. Furthermore, some liposome-specific adverse effects such as various skin reactions, and also hypersensitivity reactions, are described. We concluded that further studies with liposome-encapsulated anticancer drugs, including the development of novel liposomal formulations, are warranted to provide evidence for increased efficacy and tolerability as compared with their non-liposomal counterparts.

A dose-escalating phase I study of LiPlaCis, a liposomal formulated platinum compound, in patients with advanced solid tumors is reported in Chapter 3. This phase I dose-escalating study was conducted to define the maximum tolerated dose (MTD), the recommended phase II dose, pharmacokinetics and pharmacodynamics, as well as the preliminarily antitumor effects of a three-weekly schedule of LiPlaCis in patients with solid tumors. Although the toxicity pattern of LiPlaCis differed from cisplatin toxicity, renal damage was not prevented by the formulation. Acute infusion reactions required addition of extensive premedication that in turn could not completely prevent a high incidence of acute infusion reactions. The observed safety profile suggested no benefit over standard cisplatin formulations and LiPlaCis reformulation is required to enable further development. Recently a new phase I dose-escalating study with LiPlaCis started to find the recommended phase II dose.

In Chapter 4 a randomized, 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 is reported.
Our objectives were to (1) determine bioequivalence of paclitaxel pharmaceutically formulated as LEP-ETU and as Taxol® and (2) to assess the safety and tolerability of LEP-ETU following intravenous administration. Thirty-two of the 58 patients were evaluable patients and were analyzed for bioequivalence. The number of patients that dropped out of the study was concerning high. This high drop-out rate was most likely due to a poor patient selection. Mean total paclitaxel $C_{\text{max}}$ values for LEP-ETU and Taxol® were 4955.0 ng/mL and 5108.8 ng/mL, respectively. Mean total paclitaxel $AUC_{\text{0-\infty}}$ values for LEP-ETU and Taxol® were 15853.8 ng·h/mL and 18550.8 ng·h/mL, respectively. Ratios of the geometric means of LEP-ETU divided by Taxol® for $C_{\text{max}}$ were 97% (90% CI, 91%-103%) and for $AUC_{\text{0-\infty}}$ were 84% (90% CI, 80%-90%). These results meet the required 80-125% bioequivalence criteria. The most frequently reported adverse events after LEP-ETU administration were fatigue, alopecia, and myalgia.

**BAY 56-3722**

Chapter 5 describes a phase II study of BAY 56-3722 (formerly BAY 38-3441), a camptothecin glycoconjugate, in patients with recurrent or metastatic inoperable colorectal cancer resistant to irinotecan. Patients received BAY 56-3722 i.v. 320 mg/m$^2$ daily for 3 days every 3 weeks. Twenty-four patients received the study treatment. Triggered by adverse events in two other studies with this compound the study was put on a clinical hold while the safety data were reviewed for the entire program. We felt it was our obligation to report the fate of BAY 56-3722 and the unique situation of a clinical hold during a phase II study.

**NEW CLASSES OF ANTICANCER DRUGS**

**HDAC inhibitors**

The HDAC inhibitors recently are being investigated as possible treatments for cancer. The HDAC 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. Two of them, vorinostat and romidepsin, are already approved by the US Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma (CTCL). Romidepsin is also approved for the treatment of peripheral T-cell lymphoma (PTCL). Much research was focused on the treatment of hematological malignancies, but the last decade also clinical trials with HDAC inhibitors in solid tumors were conducted. Despite promising results in the treatment of hematological malignancies, HDAC inhibitors have generally not
been effective in clinical trials involving solid tumors. In Chapter 6, a review of the clinical trials in solid tumors of HDAC inhibitors is presented.

In Chapter 7 a phase I study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and various degrees of hepatic function is reported. This study demonstrated the impact of hepatic impairment on the systemic exposure of panobinostat and showed that patients with mild or moderate hepatic function could be safely treated with the same dose of panobinostat as patients with normal hepatic dysfunction, despite somewhat higher pharmacokinetic values.

**Cardiac glycosides**

Besides novel formulations, also ‘old drugs’ for example cardiac glycosides, could be useful in the treatment of cancer. Cardiac glycosides have a long history in the treatment of cardiac disease. However, several preclinical studies as well as two phase I studies have shown that cardenolides may also possess anticancer effects. The mechanisms of these anticancer effects may include intracellular decrease of K⁺ and increase of Na⁺ and Ca²⁺; intracellular acidification; inhibition of IL-8 production and of the TNF-α/NF-κB pathway; inhibition of DNA topoisomerase II and activation of the Src kinase pathway. In Chapter 8 a review of cardiac glycosides in cancer therapy is presented. To date only three cardiac glycosides have been developed for treatment of cancer and were tested in a phase I clinical trial to determine dose-limiting toxicities and maximum tolerated dose.

Chapter 9 reports the preclinical data and the preliminary results of a non-completed clinical phase I trial with UNBS1450, a semisynthetic cardenolide glycoside derivative. The primary endpoint of the clinical phase I was not reached due to early termination of the study for non-scientific reasons. The available preclinical work could not guide us in adapted scheduling of the patients. To establish the optimal dose and schedule of UNBS1450 for future phase I/II studies more research is necessary.

**CONCLUSION**

Many current anticancer drugs have non-ideal pharmaceutical and pharmacological properties, which can lead to adverse consequences, including lack of or suboptimal therapeutic activity, dose-limiting side effects and poor patient quality of life. In this thesis we focused on some novel formulations, especially camptothecin glycoconjugate BAY 56-3722 (formerly BAY 38-3441) and liposomal drug formulations, hoping to overcome some of
these problems. We also focused on ‘old drugs’ for new indications, as an example HDAC inhibitors and cardiac glycosides.

Unfortunately, the outcomes of some of the presented studies were disappointing: a clinical hold during the phase II study of BAY 56-3722, no benefit of LiPlaCis over standard cisplatin formulations and a non-completed clinical phase I trial with UNBS1450.

It is known that many phase I and phase II trials do not result in new treatment options used in daily practice. It is also known that publishing negative trial results is seen as less attractive and is also more difficult than publishing positive trial results. But sharing these results is essential for improving the knowledge necessary for the development of future research by the scientific community. For example a new phase I dose-escalating study with LiPlaCis started because in our phase I study a recommended dose for a phase II study was never reached which is now the aim of this phase I dose-escalating study. In addition, based on the preclinical evaluation and preliminary report of the incomplete phase I pharmacokinetic trial using UNBS1450 we now know that based on washout experiments the optimal dose may have been much higher and the optimal schedule more intensively.

Beside the disappointing outcomes of some of the presented studies, we demonstrated that LEP-ETU and Taxol® met the required 80-125% bioequivalence criteria and we showed that patients with mild or moderate hepatic function could be safely treated with the same dose of panobinostat as patients with normal hepatic function.

The reviews of liposomal anticancer drugs, HDAC inhibitors and cardiac glycosides all showed that to fulfill the high expectations of all these formulations and new drugs and to overcome the existing problems much research is still necessary.