Summary

Neuropathy and resistance to the treatment are two main burdensome consequences of chemotherapy. Neurotoxicity is the most common dose-limiting side effect of platinum compounds, which often leads to treatment withdrawal, affects the patients’ quality of life, and sometimes is irreversible. Chapter 1 shortly reviews the history of the conventional and emerging platinum-based drugs, and the characteristics of the common platinum agents in cancer treatment. More in depth, chapter 2 discusses available evidence on the pathogenesis and pathophysiology of platinum-induced peripheral neurotoxicity and discusses the characteristics and tools for its timely diagnosis. This chapter also summarizes available evidence on neuroprotective and therapeutic strategies, which indicates the heterogeneity and inconsistency of the data. Accordingly, the evidence does not clearly support the advantage of any of the tested agents to be utilized for affected patients with respect to their safety and efficacy.

Identification and quantification of adverse outcomes associated with exposures to chemotherapy agents, however, has remained widely undetermined, and is still under investigation, and numerous challenges still exist in translating biomarker research into the clinical practice. Different models have been introduced to study chemotherapy-induced neurotoxicity. The results in Chapter 3 supports the importance of the neurite outgrowth in PC12 rat pheochromocytoma cells for evaluation of the neurotoxicity. With this method, we demonstrated the neurotoxicity of oxaliplatin, bortezomib, and epothilone-B, and investigated the neuroprotective effect of amifostine. Besides, we found that upregulation of cyclin-B2 mRNA was associated with neuronal differentiation and thus oxaliplatin-induced neurotoxicity. Hence, cyclin-B2 can be used as a predictive marker.

Calcium and magnesium infusion is one of the commonly used off-label strategies by oncologists in the hope of preventing or at least, to some extent reducing the severity of oxaliplatin-induced peripheral neurotoxicity. However, consistent evidence is lacking for this method, and recent data did not support the efficacy of calcium/magnesium infusion in preventing this side effect. Chapter 4 shortly discusses this method and some tools to measure its efficacy, as well as the importance of employing suitable methodology in analysis the results.

Activation of the Akt-survival pathway is a mechanism of resistance to DNA-targeted drugs. Chapter 5 reviews the effect of common DNA-targeted anticancer drugs on Akt pathway, to see whether antagonizing the Akt survival pathway acts synergistically with the conventional treatments. Available data suggest that the mechanism of drug resistance is complex and comprises different pathways. There is evidence in favor to improve the cytotoxicity of cancer treatment. However, the available preclinical data is so heterogeneous (varying with drugs) and clinical evidence is limited.

There is evidence of a constitutive activation of Akt in pancreatic cancer. Chapter 6 describes the therapeutic potential of the novel Akt inhibitor perifosine in combination with gemcitabine in pancreatic ductal adenocarcinoma (PDAC) cells. Perifosine could effectively interfere with cell proliferation, induce apoptosis, reduce migration/invasion, and synergistically interact with gemcitabine in cells with phospho-Akt overexpression.

Increasing the formation and retention of platinum-DNA adducts by decreasing the DNA-repair enzymes may boost the antineoplastic effects of the treatment and overall survival. Chapter 7 explores the importance of protein/mRNA expression-analysis, as well as the role of polymorphism in the DNA repair enzymes in non-small cell lung cancer and PDAC.

Satraplatin is the only oral analog among platinum agents, which in case of success, may significantly decrease the burden of parenteral cancer therapy. Chapter 8 discusses our results with
regard to the potential synergism between erlotinib, an epidermal growth factor receptor inhibitor, and JM118, the active metabolite of satraplatin. The synergistic effect of the combination regimen resulted in an increased accumulation of platinum adducts in the DNA, and thereby enhanced the disruption of the cell signaling pathways, which led to growth inhibition. Consequently, we found that preincubation with JM118 followed by the JM118/erlotinib could improve the profile of the two oral agents.

Single nucleotide polymorphisms may be indicative of a shorter survival. Chapter 9 explores the role of novel predictive biomarkers for cachexia, as a direct cause of reduced quality of life and shorter survival, in PDAC. In locally advanced and metastatic PDAC, AKT1-rs1130233 and SELP-rs6136 polymorphisms were associated with the risk of developing cachexia. Moreover, AKT1-rs1130233-AA/GA genotypes were significant predictors for shorter survival, with an increased risk of death in two independent cohorts. We also found a correlation with reduced phosphorylation of Akt1 in muscle biopsies from patients harboring these particular Single nucleotide polymorphisms. Thus, it may play a prognostic role, which needs to be replicated in another independent study before utilizing it into the clinic.

Single nucleotide polymorphisms may predict brain metastases in non-small-cell lung cancer. Chapter 10 discusses some controversies between our findings and some recent data in the role of single nucleotide polymorphisms of Akt in predicting brain metastases in non-small-cell lung cancer.

Chapter 11 discusses the results presented in the present thesis compared with others in the literature. Current evidence provides many leads for further investigations to optimize the cytotoxicity of conventional antineoplastic agents, but still many questions remain unanswered with regard to the pathogenesis of chemotherapy-induced peripheral neurotoxicity and role of signaling in improving the efficacy of cancer treatment, which warrants more studies.