The Fanconi anemia/BRCA2 pathway in pancreatic cancer
van der Heijden, M.S.

Citation for published version (APA):
CHAPTER 1

INTRODUCTION

In 2005, 32,180 Americans are expected to be diagnosed with pancreatic cancer and 31,800 will die from this disease, making pancreatic cancer the fourth leading cause of cancer death in the United States\(^1\). The only effective treatment is surgical resection, which is performed in less than 20% of cases. Patients with locally advanced pancreatic cancers not amenable to resection are usually treated with chemoradiotherapy, using gemcitabine- or 5-fluorouracil (5-FU)- based regimens\(^2,3\). For pancreatic cancer with distant metastases, most clinicians consider gemcitabine to be the standard of care. However, these therapies are only marginally effective; benefit is primarily achieved in a modest extension of survival and some improvement in quality of life. Regimens combining various chemotherapeutic drugs are being investigated and often include DNA-interstrand crosslinking drugs. A rare complete response is achieved with treatment with mitomycin C (MMC)- or cisplatin- containing regimens\(^4,8\).

Clearly, new therapeutic approaches are necessary. The passed decade has witnessed a tremendous increase in knowledge about the genetic background of pancreatic cancer. Additionally, the emerging field of cancer pharmacogenomics has received much attention as an attractive new therapeutic approach, in which treatment is based on the individual genetic profile of cancer cells. Although successful examples do exist\(^9,12\), opportunities to effectively translate this approach into clinic are not often encountered, and are currently non-existent for pancreatic cancer. For example, the KRAS gene is often mutated in pancreatic cancer, causing continuous activation of the K-ras oncoprotein. Farnesyltransferase inhibitors competitively inhibit membrane anchorage of the Ras proteins (including K-ras) and had antiproliferative effects against pancreatic cancer cell lines and xenografts in preclinical models, at clinically relevant concentrations\(^13,14\). However, although tipifarnib (a farnesyltransferase inhibitor) was well tolerated in combination with gemcitabine, it did not prolong overall survival when compared to gemcitabine as single-agent therapy\(^15\). Other experimental therapies currently under
Investigation include inhibitors of the epidermal growth factor receptor (EGFR), angiogenesis inhibitors targeting the vascular endothelial growth factor (VEGF) receptor and cyclopamine, an inhibitor of sonic hedgehog signaling\textsuperscript{16-18}.

In this work, we present a new strategy to specifically target genetic defects in a subset of pancreatic cancer patients: those harboring carcinomas with genetic defects in the Fanconi anemia/BRCA2 pathway. Echoing studies of nonneoplastic cells\textsuperscript{19-22}, cancer cells defective in the Fanconi anemia/BRCA2 pathway show a remarkable hypersensitivity to DNA-interstrand crosslinking agents. Several crosslinking agents are known to be active against pancreatic cancer cells in general, and are continuously being tested and used in clinical pancreatic cancer treatment. We thus propose to specifically investigate the use of interstrand crosslinking agents in patients with pancreatic cancers defective in the Fanconi anemia/BRCA2 pathway.