Abstract

Cancer represents a significant global health challenge, with a substantially increasing incidence. There is a critical need for enhanced prevention, early detection, and improved therapeutic approaches to treat malignant diseases. While chemotherapy remains a standard treatment for many cancers, its efficacy is often limited by cytotoxic effects on healthy cells and numerous side toxicities. In response to these challenges, novel strategies such as combination therapies and drug delivery systems have emerged. In this project, we investigated the cytostatic and cytotoxic effects of two inhibitors of IAP (inhibitor of apoptosis) proteins, LCL-161 and AZD5582, and their potential to boost the anticancer activity of gemcitabine. These compounds were evaluated in five human cancer cell lines: pancreatic (PANC1, BxPC-3, MiaPaca-2), prostatic (PC-3), and breast (MDA-MB-231) carcinomas. Both IAP inhibitors demonstrated anticancer activity as single agents, with the MiaPaca-2 and BxPC-3 cell lines showing the highest sensitivity. No correlation was observed between the expression levels of IAP genes (cIAP1, cIAP2, XIAP) and the sensitivity of cell lines to IAP inhibitors. However, four of five tested cell lines possessed a consistent pattern in the expression of these three genes. IAP inhibitors were able to potentiate the cytostatic and cytotoxic activities of gemcitabine, with the most significant synergy observed in the MiaPaca-2 and MDA-MB-231 cell lines. Furthermore, HPMA copolymers bearing these drugs were synthesized and tested for toxicity in mice. These findings suggest the potential of drug delivery systems with the combination of gemcitabine and IAP inhibitors in cancer treatment, indicating the need for further investigation for their antitumor efficacy.

Keywords: gemcitabine, IAP inhibitor, HPMA copolymers, combination therapy, drug delivery, controlled drug release, anticancer activity