The combination of everolimus and zoledronic acid increase the efficacy of gemcitabine in a mouse model of pancreatic adenocarcinoma

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Résumé en anglais	Background: Gemcitabine is a standard treatment for pancreatic adenocarcinoma. Many mechanisms are involved in gemcitabine resistance, such as reduced expression of the human equilibrative nucleoside transporter 1 (hENT1) membrane transporter, deoxycytidine kinase deficiency, and changes in the signal transmission of mitogen-activity protein kinase (MAPK) and the phosphoinositide 3-kinase (PI3K) pathways. Aim: To evaluate the anti-tumor efficiency of blocking signaling pathways using combined action of gemcitabine, everolimus and zoledronic acid versus gemcitabine alone in a mouse subcutaneous xenograft. Methods: Implantations of two human pancreatic adenocarcinoma cells lines (PANC1, K-ras mutated and gemcitabine-resistant; and BxPc3, wild-type K-ras and gemcitabine-sensitive) were performed on male athymic nude mice. The mice received different treatments: gemcitabine, gemcitabine plus everolimus, everolimus, gemcitabine plus zoledronic acid, everolimus plus zoledronic acid, or gemcitabine plus everolimus and zoledronic acid, for 28 days. We measured the tumor volume and researched the expression of the biomarkers involved in the signaling pathways or in gemcitabine resistance. Results: In wild-type K-ras tumors, the combinations of gemcitabine plus everolimus; zoledronic acid plus everolimus; and gemcitabine plus zoledronic acid and everolimus slowed tumor growth, probably due to caspase-3 overexpression and reduced Annexin II expression. In mutated K-ras tumors, gemcitabine plus everolimus and zoledronic acid, and the combination of zoledronic acid and everolimus, decreased tumor volume as compared to gemcitabine alone, inhibiting the ERK feedback loop induced by everolimus. Conclusion: The combination of zoledronic acid and everolimus has an antitumor effect and could increase gemcitabine efficacy.
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