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Oral recombinant methioninase (o-rMETase) is superior to injectable rMETase and overcomes acquired gemcitabine resistance in pancreatic cancer

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Abstract

Recombinant methioninase (rMETase) was administered as an injectable drug to target methionine dependence of cancer. Recently, we observed that rMETase could be administered orally (o-rMETase) in a patient-derived orthotopic xenograft (PDOX) mouse model of melanoma. Here, we determined the efficacy of o-rMETase on a pancreatic cancer PDOX model. Forty pancreatic cancer PDOX mouse models were randomized into four groups of 10 mice each. o-rMETase was significantly more effective than i.p.-rMETase, but combination of both was significantly more effective. Acquired gemcitabine resistance is a major factor in the recalcitrance of pancreatic cancer. We tested a human pancreatic cancer cell line, which has acquired >100-fold GEM-resistance (PK-9R) than its parental cell line PK-9. In contrast to GEM, both cell lines were very sensitive to rMETase. In orthotopic nude mouse models of PK-9 and PK-9R, GEM inhibited tumor growth in PK-9 but not PK-9R. In contrast, o-rMETase could inhibit both tumors. The combination of GEM + o-rMETase could regress the PK-9 tumor and inhibit PK-9R tumor growth. The present study shows that o-rMETase is effective and overcomes acquired GEM resistance in pancreatic cancer and demonstrates the clinical potential of this strategy.

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