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Hepatic artery infusion therapy for gastro-entero-pancreatic neuroendocrine tumor liver metastases: a patient-derived preclinical study.

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BACKGROUND

Liver metastases (LM) are common in neuroendocrine tumors (NETs) and remain difficult to control. Current systemic therapies achieve modest tumor responses. Trans-arterial embolization, while effective, carries procedural morbidity and requires repeated interventions. Hepatic artery infusion pump (HAIP) therapy enables highly selective, high-concentration intrahepatic drug delivery with minimal systemic toxicity, with well-established efficacy in colorectal LM. Its potential in NETs has not been systematically studied. The optimal agents for hepatic arterial delivery in this histology are unknown. A critical first step is to characterize NET drug sensitivity to candidate HAIP-deliverable agents, alone and in combination with approved systemic therapies.

METHODS

Using an integrated platform combining a large NET biobank with patient-derived organoid (PDO) and avian xenograft (PDXovo) models, we will test HAI-deliverable agents: floxuridine (FUDR), paclitaxel, dacarbazine, gemcitabine, and streptozocin. First, PDOs from liver will be treated with each agent across multiple concentrations and combinations, with sunitinib as positive control and normal liver and cholangiocyte lines as toxicity controls. Drug efficacy will be assessed by apoptosis (Annexin V), metabolic activity (ChromaLive Yellow), and endoplasmic reticulum stress (ChromaLive Red) using confocal imaging. Second, Avian patient-derived zenografts (PDXovos) will quantify intratumoral drug penetration using fluorescent drug probes and immunostaining. They will be used to validate top-performing agents, with tumor volume and blood flow quantified by high-frequency ultrasound and histologic markers including chromogranin A, Ki-67, and cleaved caspase-3. The two most effective agents will be tested in cross-titration with approved systemic therapies (sunitinib, cabozantinib, everolimus, Lutathera).

RESULTS

We plan to study liver metastasis-derived PDOs from 12 patients (6 male, 6 female) and PDXovos from 6 patients (3 male, 3 female) with gastro-entero-pancreatic (GEP)-NETs. This will build on a platform that has generated over 10,000 PDOs and 100 PDXovos from prior GEP-NET specimens with >95% model generation success. Treatment of the first PDO cohorts is now underway, with initial drug-response rounds currently in progress. Initial results are expected in October 2026.

CONCLUSIONS

This will be the first systematic, mechanistically grounded evaluation of HAI therapy in GEP-NETs, to define which agents, alone or combined with contemporary systemic therapy, warrant clinical testing in unresectable NET liver metastases. Pairing an established HAIP program with a successful patient-derived NET models platform provides a direct path to early-phase trials.

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