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Novel mouse models of hepatic artery infusion

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ABSTRACT

Background: The liver has unique anatomy in that most blood flow to normal hepatocytes is derived from the portal venous system, whereas liver tumors obtain their nutrient blood supply exclusively from the hepatic artery. The focused arterial delivery of anticancer agents to liver tumors has been performed for decades; however, preclinical models to standardize drug regimens and examine novel agents have been lacking. The purpose of this study was to establish preclinical hepatic artery infusion (HAI) models in a mouse and to evaluate the safety and delivery capability of the models.

Material and methods: C57BL/6 and BALB/c mice were used to develop models of HAI via the hepatic artery (HA), superior pancreaticoduodenal artery (SPDA), or lienogastric artery (LGA). Success rates, distribution of perfusion, and associated morbidity and mortality were analyzed between groups.

Results: All three models were feasible and reproducible in mice, and there was no statistical difference on body weight change between models. The HA model had a 13.3% mortality from acute liver failure, and the SPDA model demonstrated duodenal and pancreatic toxicity. SPDA and LGA routes had the highest success rates (96.7% and 91.4%, respectively) with low mortality, better drug delivery, and preserved physiologic liver function compared with the HA model.

Conclusions: The optimal route of HAI was mouse breed specific; SPDA access in BALB/c mice, and the LGA access in C57BL/6 mice. The described techniques serve as a reproducible platform for the identification and characterization of therapeutics for diverse metastatic liver tumors.

Introduction

The liver is a frequent site of metastases from a variety of cancers including gastric, breast, melanoma, and pancreatic with colorectal cancer being the most common source.[1-5] Although surgical resection of metastatic lesions has proven effective and improves overall survival, many patients develop extensive or unresectable diseases not amenable to

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surgery. Regardless of the tumor source, the 5-y survival rate is less than 10% in patients with unresectable liver metastases.[6-10] Although systemic chemotherapy may prolong overall survival in patients with unresectable metastatic disease, intravenous chemotherapy and/or radiation therapy does not achieve a cure in these cases and is limited by systemic toxicity and cumulative dose.

Hepatic artery infusion (HAI) chemotherapy for the treatment of liver cancers has been investigated for over 4 decades.[11] The rationale for HAI is that hepatic metastases receive their nutritive blood supply from the hepatic arterial system.[12] HAI concentrates chemotherapy agents with direct delivery to the tumor bed. In addition, typical drugs used for HAI have a high first-passage hepatic clearance, resulting in less systemic exposure.[13] Although HAI chemotherapy as a regional therapy has been used clinically for decades in the treatment of both primary and metastatic cancers of the liver, significant toxicity remains a concern, and clinical results have been mixed in terms of improved survival outcomes.[14-20]

What has been lacking in the field is a reproducible and stringent preclinical animal model. Experimental models with pigs, rabbits, or rats have been used previously, but cost, animal size, and a lack of syngeneic tumor lines limit their utility.[21-23] A mouse model would be ideal as there are multiple cell lines and techniques to generate hepatic metastases.[24] Moreover, as tumor cell lines can be syngeneic in mice, the immune system remains intact and can be investigated for contributions toward antitumor effects of HAI. Several requirements are necessary for an optimal preclinical HAI model including (1) reproducibility, (2) postprocedure liver integrity, and (3) clinical similarity. We sought to design a mouse model of HAI that could serve as a platform for preclinical testing of novel agents and treatment conditions. Herein, three individual methods of HAI delivery in mice are reported and compared for feasibility, morbidity, and toxicity.

Materials and methods

Mice

Female C57BL/6 and BALB/c mice aged 8-12 wk were purchased from Charles River (Kingston, NY). Mice were fed a standard laboratory diet and housed under standard light and accommodation conditions. All experimental protocols were approved by the Roswell Park Cancer Institutional Animal Care and Use Committee.

HAI procedures

HAI was performed by a single investigator (M.K.) with three different approaches that included the hepatic artery (HA) directly, the HA via the superior pancreaticoduodenal artery (SPDA) or via the lienogastric artery (LGA) (Fig. 1). Non–tumor-bearing mice received inhaled anesthesia with isoflurane (induction with 4%, maintenance 1.5%) to an appropriate level. Mice were placed on a warming platform to maintain normothermia throughout the procedure under a dissecting microscope (magnification × 6.5 ~ ×45) (VWR, West Chester, PA). The abdomen of the mouse was prepped with alcohol and betadine, and a 3-cm longitudinal midline incision was made using scissors, and then the xiphoid process was resected to obtain a wide working field. The abdomen was opened using two 5-0 silk sutures as anchors, the viscera were gently displaced to the left side of the abdominal cavity, and the portal vein (PV), abdominal inferior vena cava, bile duct, and celiac

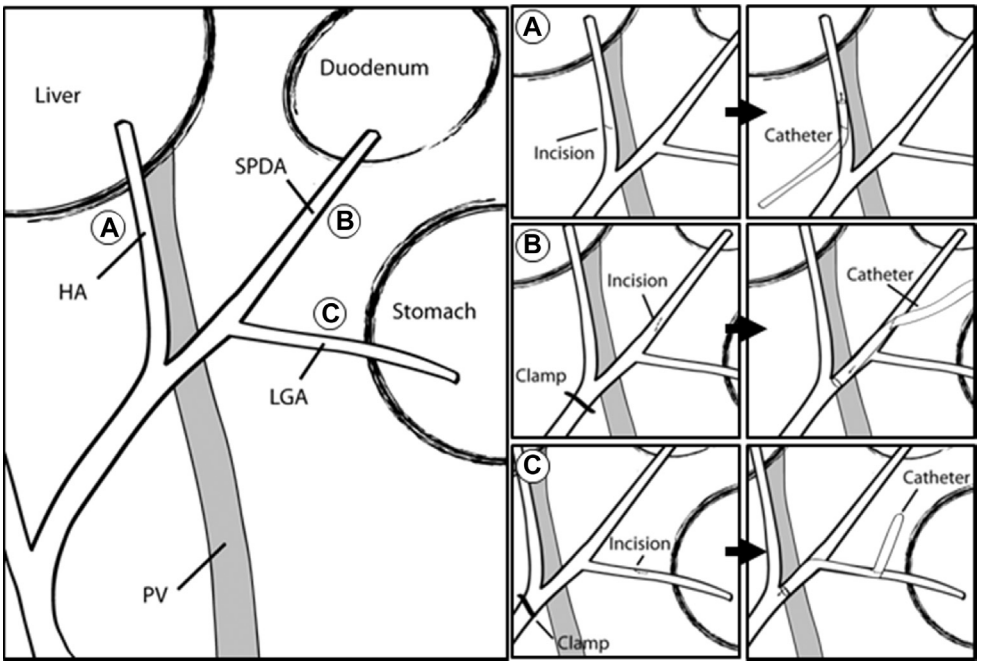

Fig. 1 – A schematic diagram of three models for HAI. A, The HA access; B, The SPDA access; C, The LGA access. The duodenum was displaced superiorly.