Hepatic-directed Therapies in Patients with Neuroendocrine Tumors

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KEYWORDS

• Hepatic-directed therapies • Neuroendocrine tumors
• Therapy response and survival • Metastases • Intra-arterial

KEY POINTS

- Intra-arterial therapies for unresectable liver metastases from neuroendocrine primary tumors are supported by level 2a medical evidence (National Cancer Institute) regarding symptom control and imaging response.
- There is insufficient medical evidence showing which intra-arterial therapy (transarterial embolization [TAE], transarterial chemoembolization [TACE], transarterial radioembolization [TARE]) provides the highest response rate, progression-free survival, or overall survival.
- TARE produces less toxicity and has similar efficacy to TAE and TACE.
- Intra-arterial therapies are an important aspect of managing metastases from neuroendocrine tumor liver disease in all stages of disease, including asymptomatic, first-line, salvage, and palliation scenarios.

INTRODUCTION

Neuroendocrine tumors (NETs) of the gastrointestinal (GI) tract have a propensity for producing hepatic metastases. The liver is the most common site of metastatic dissemination from NETs and this occurs in from 10% to 65% of cases.[1,2] Most GI NETs arise from the foregut or midgut, are malignant, and can cause severe debilitating symptoms adversely affecting quality of life.[3–5] Aggressive treatments to reduce symptoms have an important role in therapy.

Patients with GI NETs usually present with inoperable metastatic disease and severe symptoms from a variety of hormones and biogenic amines. Less than 10% of patients with small bowel and colon NETs experience what is referred to as carcinoid syndrome,[5] the symptoms of which are episodic flushing, bronchoconstriction

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(wheezing), diarrhea, and eventually heart valve dysfunction. Disease progression differs widely[4] but the overall median survival is 75 months.[6] With metastatic disease, 5-year survival rates are less than 20%.[7,8] In patients with advanced, unresectable liver metastases the treatment challenge is directed toward palliating symptoms and slowing down or stabilizing tumor growth.

Metastases from NETs (mNETs) to the liver represent a significant clinical entity, and multiple treatment modalities have been used, engaging multidisciplinary teams of gastroenterologists, diagnostic radiologists, oncologists, surgeons, and interventional radiologists. Management modalities used in patients with unresectable metastatic disease, described in other articles of this issue, include systemic chemotherapy, somatostatin analogues, cryotherapy, radiofrequency ablation, peptide receptor radiation therapy, percutaneous alcohol injection, and hepatic transplantation.[3,9–19]

This article describes intra-arterial hepatic-directed therapies for mNETs, a group of treatments in which the therapeutic and/or embolic agents are released intra-arterially in specific hepatic vessels to target tumors.

HEPATIC ANATOMY AND RATIONALE FOR INTRA-ARTERIAL THERAPIES

The unique double vascular supply of the liver, through the portal vein and the hepatic artery, and the predominantly arterial irrigation of liver tumors are the basis for intra-arterial therapies.[20] Three types of hepatic arterial embolization techniques are currently in use: transarterial embolization (TAE); transarterial chemoembolization (TACE), which includes using drug-eluting beads (DEBs); and radioactive microsphere release into arteries. Radioactive microsphere release is also known as radioembolization, transarterial radioembolization (TARE), and selective internal radiation therapy (SIRT).[8,21–23] TARE is a form of brachytherapy in which intra-arterially injected microspheres loaded with yttrium 90 (^{90}Y) serve as sealed sources for internal radiation via a near-pure beta-decay isotope with limited tissue penetrance in the range of 2 to 3 mm.[21,22]

A well-established body of literature has described the process of tumoral angiogenesis occurring exclusively from the hepatic arterial supply.[20,24,25] Circulation from the portal vein does not provide a significant contribution to tumor perfusion. Catheter-based hepatic arterial administration of therapy therefore results in a preferential deposition of a drug/particle into the tumor vasculature, which minimizes liver parenchymal exposure. Carrier-based delivery of chemotherapeutics is achieved via either the infusion of a lipiodol/water-based emulsion or via statically charged DEBs.

INTRA-ARTERIAL THERAPIES REVIEW

The various facets of intra-arterial therapies are discussed here, including their mechanisms of action, patient eligibility factors, and common toxicities arising from liver treatment, as well as therapy response evaluations and retreatment factors.

Mechanisms of Action

Arterial embolization, or TAE, is the general term for the procedure by which a catheter is inserted into an artery percutaneously, eventually directly accessing the hepatic artery. Contrast is subsequently injected via the catheter to verify its position relative to the vascular distribution of the target tumor. Contrast is frequently used during and after delivery of the therapeutic agent to monitor progress of treatment and verify completion of intended effect (ie, stasis or pruning of tumor arteries).

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