Transarterial Therapy for Colorectal Liver Metastases

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KEYWORDS

- Hepatic arterial therapy (HAT) • Chemoembolization • Hepatic artery infusion (HAI)
- Colorectal liver metastases • Surgical resection • Yttrium-90
- Drug-eluting beads (DEB)

KEY POINTS

- Hepatic arterial therapy (HAT) represents a minimally invasive fluoroscopy-guided transarterial catheter-directed therapy that has been used for the treatment of colorectal liver metastases; its primary goal is high-dose local regional drug delivery. Therapy-associated complication rates are low.
- New HAT-drug-eluting bead (DEB) technologies lead to significantly increased cytotoxic drug concentrations in the target liver metastases with lower systemic toxicity than systemic treatments.
- Repeat HAT-DEB procedures augment tumor response to treatment. Repeat Yttrium-90 treatments should be performed with the understanding that repeat treatments increase the possibility of producing durable refractory radiation-induced liver dysfunction.
- HAT may augment the results of first-line systemic chemotherapy in the treatment of patients with unresectable colorectal liver metastases. It may represent a valuable tool in the preoperative management of potential surgical candidates as a method for downsizing and for early conversion to resectability without adverse effects associated with systemic chemotherapy.
- HAT could potentially be used after surgery or ablative therapy to prevent local recurrence with the aim of improving overall survival without major side effects.

BACKGROUND

Colorectal liver metastases (CLM) represent the fourth most common malignancy, and the second most common cause of cancer-related death in Western countries. The presence and extent of liver metastases are major prognostic factors with respect

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to overall survival (OS). At the time of diagnosis of colorectal cancer, 25% to 50% of patients exhibit liver metastases. Furthermore, up to 80% of patients diagnosed with colorectal cancer will develop liver metastases on follow-up evaluation. Because the microstructure of the liver is an effective tumor cell barrier, early distant metastasis due to hematogenous spread is rare. A variety of therapies exist for the treatment of CLM—surgical resection, systemic chemotherapy (CTx), molecular substances, and local ablative treatments. What constitutes the optimal treatment strategy for a given patient depends on tumor stage, mutation status, sequence and pattern of metastases, performance status, and patient preference.[1,2]

Surgical resection is currently accepted as optimal first-line treatment. Resectability with curative intent can be characterized by 5 isolated metastases per liver lobe or less, at least 2 tumor-free adjacent liver segments, and a volume of the liver remnant greater than 20% by reference to the initial liver volume.[3,4] At the time of diagnosis, less than 20% of patients have resectable CLM,[3,4] and 60% to 80% of those undergoing resection will develop recurrent colorectal metastases at follow-up, of which half have a recurrence within the liver.[5,6]

The greater than 80% of patients who do not qualify for CLM resection at the time of diagnosis receive CTx and/or biologic therapy according to the current available European guidelines.[1] Currently, 5-fluorouracil (5-FU) -based regimens consisting of 5-FU, irinotecan, and/or oxaliplatin (eg, FOLFOX, FOLFIRI, and FOLFOXIRI) result in response rates and median OS of 40% to 57% and 15 to 20 months, respectively, but reported 5-year OS rates are still close to 0%.[1,2,7–12] On average, the median OS of patients with stage IV colorectal cancer approximates 21 months with multiagent chemotherapy (intravenous 5-FU plus irinotecan/oxaliplatin). The introduction of molecular substances such as antiepidermal growth factor receptor (EGFR) and anti-vascular endothelial growth factor (VEGF) antibodies have further improved outcomes after administration of systemic therapies. Controlled trials showed that the addition of a monoclonal antibody to CTx regimens increased OS to more than 24 months.[1,13]

Current evidence suggests that CTx with or without the use of biologic agents followed by liver resection is safe and effective for selected patients with initially unresectable CLM.[14–18] Use of hepatic arterial therapy (HAT) toward the same end represents an enticing concept, because it allows for markedly higher concentration of drugs or radiation therapy within target liver area, while decreasing the systemic toxicity and adverse effects of CTx or external beam radiation therapy.[19]

TRANSARTERIAL HEPATIC THERAPY

Rationale

Although normal liver parenchyma is largely supplied by the portal vein, malignant liver tumors derive their blood supply from hepatic arterial branches.[20] Thus, transarterial drug delivery into the liver allows a considerably increased local drug concentration/radiation dosage compared with CTx/external beam radiation therapy. At the same time, healthy nonaffected liver parenchyma can be spared, and the liver toxicity that is observed after systemic applications is avoided or at least minimized. Chemotherapy-associated liver injury (CALI; eg, sinusoidal obstruction syndrome [SOS] and nonalcoholic steatohepatitis [NASH])—are relevant limitations to cytotoxic therapy that impact preoperative treatment plans. Hepatic steatosis without inflammation (simple steatosis) may occur with chemotherapy. SOS may occur with oxaliplatin treatment, with increased severity associated with prolonged treatments (>6 cycles). Bevacizumab can be used safely in the preoperative setting when discontinued at

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