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PERSPECTIVES

Hepatic Arterial Infusion Chemotherapy for Hepatocellular Carcinoma: A Three-Dimensional Visualization Perspective

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Abstract: In Asia, hepatic arterial infusion chemotherapy is an alternative therapeutic option for hepatocellular carcinoma (HCC). However, the current application of HAIC lacks precision, as drug dosages are typically calculated based solely on body surface area. This approach often results in underdosing for patients with larger liver tumors or greater liver volume and overdosing for those with smaller liver tumors or reduced liver volume. Consequently, determining drug dosages according to the specific target volume requiring treatment may enhance individualized and standardized therapy for HCC, aligning with the principles of precision oncology.
Keywords: hepatic arterial infusion chemotherapy, hepatocellular carcinoma, target volume, precision

Current Situation of Liver Cancer in China in a Global Context

Primary liver cancer remains one of the most common malignancies worldwide and poses a serious threat to human health. According to Global Cancer Statistics 2022, liver cancer accounted for 865,269 new cases and 757,948 deaths globally, representing a significant disease burden.[1] In China, data from the National Cancer Center identified primary liver cancer as the fourth most prevalent malignancy (367,700 new cases) and the second leading cause of cancer-related death (316,500 deaths) in 2022.[2] Hepatocellular carcinoma (HCC) accounts for approximately 90% of all primary liver cancers. Unfortunately, fewer than 30% of HCC patients are candidates for curative surgical resection at the time of diagnosis. Even among those who undergo surgery, the high rate of postoperative recurrence remains a critical challenge. A multicenter, Phase III, randomized study revealed that the 3-year disease-free survival (DFS) rate in HCC patients with microvascular invasion who underwent liver resection without adjuvant therapy was only 22.6%.[3] Thus, the high incidence, high mortality, and high recurrence rate of HCC have made it an urgent public health concern in China.

Application of Hepatic Arterial Infusion Chemotherapy (HAIC) in HCC: Therapeutic Benefits and Limitations

HAIC has been utilized for decades in treating liver cancer, and its application in HCC has attracted increasing attention, particularly over the past five years. A PubMed search from January 1, 2024, to November 2, 2024, using the keywords "HCC" and "HAIC" in the "Title/Abstract" fields, identified 82 relevant publications. In Asia, HAIC is recognized as an alternative therapeutic strategy for patients with unresectable HCC and is widely recommended in multiple HCC guidelines.[4,5] Recently, Chinese researchers have pioneered the use of HAIC with oxaliplatin, fluorouracil, and leucovorin (HAIC-FOLFOX), demonstrating significantly improved overall survival compared to transarterial chemoembolization in patients with large, unresectable HCC.[6] Additionally, HAIC-FOLFOX has been shown to enhance postoperative DFS in patients with HCC complicated by microvascular invasion.[3] When combined with systemic therapies such as

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tyrosine kinase inhibitors (TKIs) or programmed death-1 (PD-1) inhibitors, HAIC has shown promising efficacy in advanced HCC, with some patients successfully undergoing conversion surgery.[4,7]

Despite these advances, the current application of HAIC lacks precision from a personalized medicine standpoint. HAIC dosing is typically determined based on BSA, following systemic chemotherapy dosing guidelines, rather than considering the locoregional nature of the therapy. This approach overlooks the hepatic pathophysiological changes associated with tumor burden heterogeneity and variations in liver volume. Studies have demonstrated that BSA has limited predictive value for liver volume, and its accuracy is significantly influenced by factors such as inflammation, neoplastic infiltration, and other disease states.[8] Consequently, BSA-based dosing can lead to considerable variability in treatment outcomes, potentially compromising both therapeutic efficacy and safety. While clinicians have recognized this limitation and often adjust HAIC dosages based on tumor size and vascular supply, these adjustments are primarily based on clinical experience rather than standardized protocols. For example, oxaliplatin doses may vary between 85 mg and 135 mg empirically.[3,4,6]

Although HAIC enhances drug delivery to liver tumors, allowing for high local concentrations of chemotherapy agents, reliance on BSA for dose calculation may result in suboptimal outcomes. Patients with larger tumors or greater liver volume may receive insufficient drug doses, potentially reducing treatment effectiveness. Conversely, patients with smaller tumors or lower liver volume may be exposed to excessively high drug concentrations, increasing the risk of adverse events such as severe abdominal pain, hepatic toxicity, and myelosuppression. These complications may necessitate treatment interruption or discontinuation. Li et al observed that severe abdominal pain was more common in patients whose tumors had significantly reduced in size. They recommended dose adjustments, including reducing oxaliplatin to 85 mg/m² in patients with significantly shrunken tumors or small HCC.[6] Additionally, when HAIC is combined with systemic therapy, the risk of adverse events increases, necessitating drug dose adjustment, treatment interruption, or discontinuation in a subset of patients.[9]

Advances in Three-Dimensional (3D) Visualization in Hepatobiliary Surgery: Technological Developments and Clinical Implementation

Historically, with conventional two-dimensional (2D) imaging modalities, such as ultrasonography and contrast-enhanced computed tomography (CT), clinicians encountered substantial barriers in acquiring precise quantification of hepatic neoplasms and liver volumes. However, recent advancements in digital medical technology have facilitated the widespread application of 3D liver visualization in surgical planning. This technology has demonstrated substantial clinical value in calculating liver volume, guiding live donor liver transplantation, and measuring liver volume in blood flow areas.[10,11] Importantly, 3D visualization offers pathway guidance for cryoablation using argon-helium technology and radiofrequency ablation for liver tumors, allowing accurate assessment of ablation zones induced by electrode probes.[11] Multiple software solutions are now available for 3D liver visualization, aiding in the diagnosis and staging of complex liver tumors and the preoperative simulation of liver resections. Some of these platforms have been independently developed by Chinese researchers. Clinicians and medical imaging centers using spiral CT scanners with native 3D reconstruction capabilities or open-source 3D reconstruction platforms (such as the 3D Slicer image computing platform) can generate liver models for volumetric assessment. These models help quantify tumor and liver volumes and address economic barriers associated with the acquisition of proprietary 3D visualization software.

Integration of 3D Visualization Technology into HAIC: A New Precision Strategy

3D visualization technology allows for accurate quantification of hepatic tumor volume burden, vascular perfusion territories, and total liver volume. Integrating 3D visualization into HAIC enables volumetrically guided dosing, promoting individualized and standardized treatment for patients with HCC, and maximizing the therapeutic value of HAIC. Building on established HAIC catheterization techniques,[4] we propose a novel drug dosing protocol based on the volumetric assessment of the treatment target. The following strategies are recommended:

1. Solitary Hepatic Tumor: A catheter is selectively inserted into the main artery supplying the tumor. HAIC dosage is calculated based on the tumor volume.
2. Multiple Tumors Confined to One Liver Lobe: The catheter is positioned in the hepatic artery supplying the affected liver lobe. Dosage is calculated based on the volume of the involved liver lobe.
3. Tumors Involving Both Liver Lobes: Catheterization of the proper hepatic artery is recommended. HAIC dosage is determined based on the total liver volume.
4. Postoperative Adjuvant Therapy: Catheterization of the proper hepatic artery is performed. Residual liver volume is assessed via CT at least one month postoperatively to guide dosing decisions. Variations in residual liver volume due to regeneration and edema may affect measurement accuracy during early postoperative assessments.

Dosage adjustments should comprehensively consider hepatic functional reserve and patient performance status. We believe that future precision HAIC protocols for HCC will integrate multidimensional quantitative parameters, encompassing both liver volume and function, to establish a more scientific and individualized drug dosing model.

Conclusion

HAIC is an important treatment modality for hepatocellular carcinoma, particularly in Asia. However, current practices relying on BSA for dose calculation fail to address tumor heterogeneity and liver volume variations, limiting treatment efficacy and safety. The integration of 3D visualization technology offers a promising approach for individualized and standardized HAIC dosing based on volumetric analysis. This strategy aligns with the principles of precision medicine and may optimize therapeutic outcomes for patients with HCC. Further research and clinical validation are needed to establish standardized volumetric dosing protocols for HAIC in the precision oncology era.

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Disclosure

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