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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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EDITORIAL

Improving clinical outcomes of patients with hepatocellular carcinoma: Role of antiviral therapy, conversion therapy, and palliative therapy

Vishal G Shelat

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Abstract

In this editorial, I comment on three articles published in the recent issue of the *World Journal of Gastrointestinal Oncology*. Hepatocellular carcinoma (HCC) is an important public health concern, and there are three articles on the theme of HCC in this issue. I focus on the articles by Mu *et al*, Chu *et al*, and Ma *et al* for this editorial. While these articles may be considered as low-quality evidence, and the results cannot be generalized to non-hepatitis-B or C virus patients, the discussion of the results is important. In addition, though all the articles are from China, the relevance of the results is not minuscule. As resection is the main form of curative treatment modality owing to a donor liver shortage, surgeons need to be aware that preoperative long-course antiviral therapy can improve clinical outcomes by reducing postoperative liver dysfunction and recurrence of HCC following resection. Similarly, patients with super-giant HCC (defined as ≥ 15 cm diameter) should also be carefully considered for liver resection, and if it is unresectable upfront, then a combination of liver-directed therapy and systemic therapy may downstage HCC. If, following downstaging, the patient qualifies for liver resection based on locally prevalent resectability criteria, then such therapy is labelled as conversion (from unresectable to resectable) therapy. In unresectable patients treated by a combination of treatment options, serological markers like neutrophil-to-lymphocyte ratio and alpha-fetoprotein are reported to predict treatment responses, thus enabling personalized medicine.

Key Words: Antivirals; Chemoembolization; Conversion therapy; Hepatocellular carcinoma; Lenvatinib; Neutrophil-to-lymphocyte ratio

Core Tip: Hepatocellular carcinoma (HCC) is a common cancer, and the treatment approaches are evolving. The outcomes of liver resection patients can be improved by early diagnosis, robust implementation of screening programs, and pre-operative antiviral therapy for patients who qualify for it. In patients managed with multimodality treatment, downstaging and conversion to surgical resection remain possible. Simple serological markers can be useful for predicting the response to curative or palliative intent treatment of HCC patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) remains within the top five causes of cancer-related mortality globally and, thus, is an important public health concern[1]. Although nonalcoholic fatty liver disease-associated steatohepatitis and resultant hepatic fibro-cirrhosis is increasingly relevant as an aetiology of HCC, hepatitis B virus remains the dominant aetiology, especially in the global east where the HCC burden is higher than in the west[2]. Despite improved diagnostics, better implementation of screening programs, advances in precision oncology, and refinements in surgical procedures with the adoption of innovative technology, the improved perioperative outcomes have not translated into proportionately improved oncological outcomes[3]. As surgery remains the primary curative modality for HCC, it is essential to study how perioperative outcomes can be improved. The study by Mu *et al*[4] is important as it sheds light on the benefit of preoperative antiviral therapy, comparing its long-term and remedial (short-term) administration. Despite screening programs and improved diagnostics, detecting HCC at an advanced stage or as a large-diameter tumour is commonplace. Thus, the study by Chu *et al*[5] is important as the authors report a patient with giant HCC who was successfully operated after a period of conversion therapy. This report illustrates the importance of multidisciplinary team management and customized patient-specific treatment plans to improve oncological outcomes. Finally, in patients for whom a cure is not possible, palliative treatment with liver-directed chemo or radioembolization has been known to improve survival outcomes with a reasonable quality of life[6,7]. Thus, the study by Ma *et al*[8] is important as the authors demonstrate combination treatment modalities improve survival outcomes and report predictive factors which can inform the clinical decision for treatment recommendations in non-resectable HCC patients. This editorial discusses the pertinent issues relevant to the three articles, complements the authors' discussions, and includes some personal viewpoints.

ANTIVIRAL THERAPY IN HEPATITIS B PATIENTS WITH HCC

The scope of this editorial excludes comments on the general indications and role of antiviral therapy in all patients with hepatitis B or hepatitis C virus infections. It is limited to the context of HCC patients who undergo liver resection and require antiviral treatment. In many healthcare service contexts, a patient with hepatitis B or C virus is managed by a medical expert, typically a gastroenterologist or hepatologist. Only when a diagnosis of HCC is either suspected or confirmed is a surgical opinion solicited. When a patient is referred to the surgeon, the surgical team focuses on the patient's fitness, liver function, and oncological staging to assess resectability. Thus, antiviral care is managed by the medical team and surgical care is managed by surgical team and the two teams must communicate with one another. Regarding antiviral treatment, although it is assumed that a patient will be prescribed and treatment compliant, it is not always so. Various reports estimate adherence to antiviral treatment to be approximately 75%-80%[9]. Noncompliance increases the risk of HCC and is a risk factor for post-hepatectomy liver dysfunction and recurrence of HCC[10,11]. Hence, it is essential that once a patient is judged eligible to receive antiviral therapy, the treatment continues during the perioperative phase. However, some patients will not be taking these medications, and hence, it is important that the surgical team engages the medical team regarding rescue or remedial peri-operative antivirals to reap whatever benefits they provide. In a retrospective case-control study, the authors reported results that echo the common sense logic that adequate treatment is better than some treatment. Thus, though rescue or remedial antiviral treatment has some benefits, it is essential to ensure that patients receive the full dose and duration of pre-operative antiviral treatment before resection. At this time there are no data to support delaying surgical treatment until few weeks or a couple of months for antiviral treatment to be initiated. The tumour-doubling time is more than 100 d, and Cheo *et al*[12] reported that a delay of 90 d resulted in noninferior oncologic outcomes. However, because of patient and next-of-kin anxiety and heterogenous tumour behaviour with risk of disease progression, multidisciplinary teams have to consider whether delaying surgery and administering antiviral therapy would improve outcome or worsen them[12]. In general, a balanced approach, not rushing or expediting surgery and even considering delaying it for a few more days to a couple of weeks and starting antivirals before surgery seems reasonable in patients who qualify for antivirals. The benefit of antiviral therapy is also shown in another article of this journal volume where Chu *et al*[5] reported that combination of perioperative systemic and liver-directed therapy along with sofosbuvir/velpastasvir fixed-dose combination drug downstaged a patient with advanced hepatitis C virus-associated HCC.

CONVERSION THERAPY FOR HCC

HCC patients with preserved liver function are unique as they do not have typical symptoms of abdominal pain, have a functioning gastrointestinal tract and thus remain well nourished, and generally survive a few years despite inoperable or unresectable disease. Although patients with advanced disease are offered palliative therapies, these modalities have nothing to palliate but rather confer survival gains[13]. In addition, the improved understanding of HCC molecular biology, advances in immunotherapy and tyrosine kinase inhibitor drug discovery, and clinical experience that some patients respond exceptionally well to palliative therapy that they fall under the expanded resection criteria, have led to the concept of conversion therapy in HCC[14]. In general, systemic therapies are slow to permeate HCC treatment algorithms. Chu *et al*[5] described a hepatitis C virus-associated HCC patient treated by multimodality therapy who converted from inoperable to resectable disease and illustrates the efficacy of modern systemic therapy in HCC. Although the patient experienced dose-limiting treatment-related side effects, the tumour decreased from 15 cm to 11 cm, and when resected at 21 mo, the tumour histology revealed a complete treatment response and no viable disease. Typically, HCC tumour size has not received the credit that it rightfully deserves, unlike in other solid abdominal tumours[15]. It is a matter of common sense that a larger size distorts anatomy, increases the encroachment and proximity of the tumour to major blood vessels, biliary radicles, or the liver hilum, reduces the operative field area, makes it difficult to manipulate and handle the liver tumour-specimen, and thus increases operative technical difficulty. In patients with super-giant HCC (defined as ≥ 15 cm in diameter), size was a predictor of poor oncological outcomes[16]. In addition, neo-adjuvant treatment may be recommended for a large HCC may be even if upfront it is resectable. In patients with an HCC tumour of ≥ 5 cm in diameter, preoperative neoadjuvant transarterial chemoembolization has been shown to improve disease-free survival. Thus, management plans should consider the tumour size[17]. When the advances in systemic therapies are considered in tandem with advances in radiation oncology and surgical techniques such as associated liver partition and portal vein ligation for staged hepatectomy, it is anticipated that the hepatobiliary surgeon will increasingly be faced with a patient profile that is not treatment naïve, including redo and repeated liver resections[18,19]. The case report by Chu *et al*[5] includes the patient's age, sex, institution name, and surgery date. It is my view that this information can serve to identify the patient, thus breaching privacy. It is essential that authors, reviewers, the journal editorial office remain cognizant of safeguarding patient privacy. Additionally, both Mu *et al*[4] and Chu *et al*[5] fail to report the 30-d and 90-d post-hepatectomy outcomes, which are integral to scientific reports. It is essential and should be a matter of routine for every liver resection report to include these details.

PROGNOSTIC INDICES IN THE MANAGEMENT OF UNRESECTABLE HCC

A combination of liver-directed treatment approaches and systemic therapy can manage patients with unresectable HCC who are not eligible for liver transplantation. The realm of systemic therapy is rapidly evolving, and transarterial chemo or radioembolization has prevailed as the most common liver-directed therapy. Given intratumoural heterogeneity and the inherent variability in tumour biology across diverse patient populations, it is crucial to identify the groups of patients who would benefit the most. Response to treatment is an important ingredient in predicting oncological outcomes, and if simple serological markers could predict this, they are welcome. Thus, the study by Ma *et al*[8] is an important contribution to the literature. The authors report a retrospective cohort of unresectable HCC patients treated with systemic and liver-directed therapies and conclude that the neutrophil-to-lymphocyte ratio (NLR) and alpha-fetoprotein help predict the treatment response[6]. Over the past decades, many serological markers have been proposed as having clinical value in outcome prediction. For example, the platelet-to-lymphocyte ratio and albumin-bilirubin index have been reported to aid in predicting oncologic outcomes of patients undergoing liver resection or treated by liver-directed and/or systemic therapy with palliative intent[20,21]. The authors used an NLR cutoff value of 3, which is consistent with the published literature[22]. Put simply, a higher lymphocyte count means a higher immune response against the tumour antigens. The lymphocyte count is the denominator, and a lower NLR is better. A high neutrophil count means higher acute inflammation, and a lower NLR is worse. Thus, it is also logical that perioperative steroid modulating inflammatory response following liver resection has been beneficial[23]. As the Barcelona Clinic for Liver Cancer staging system is very restrictive and limits certain stage-B patients from receiving liver resection, the results of this study should not be generalized to all unresectable patients[2].

CONCLUSION

The three articles cover a wide array of issues pertinent to HCC management. As all three publications are reported from mainland China and include a predominantly hepatitis B virus population, the results should be interpreted cautiously. Additionally, a solitary case report of good outcomes leading to successful conversion of hepatitis C virus HCC patients, while encouraging, should be interpreted cautiously. Clinicians should embrace evidence-based medicine and formulate management plans after multidisciplinary team discussions. It is essential that where the boundary of evidence fades, clinicians remain open-minded and do not offer their patients available treatment options simply because there is no evidence as "absence of evidence is not evidence of absent benefit." Thus, it remains an ethical obligation incumbent on every hepatobiliary surgeon to recruit patients in ongoing clinical research trials and advocate for the patients to push the frontiers of care provision and contribute to improving HCC survival outcomes.

FOOTNOTES

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