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EDITORIAL

Impact of liver metastasis on immunotherapy in gastric carcinoma

Mushtaq Chalkoo, Mohd Yaqoob Bhat, Yaser Hussain Wani

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Abstract

The editorial discusses the impact of liver metastasis on immunotherapy efficacy in gastric cancer (GC) patients. Liver metastasis can hinder the effectiveness of immunotherapy by altering the immune microenvironment, leading to systemic loss of T-cells and reduced treatment response. Studies suggest that liver metastases serve as a negative baseline factor for immunotherapy efficacy, resulting in poorer progression-free survival and objective response rates. Strategies such as liver-mediated radiotherapy may help improve treatment outcomes by reshaping the liver's immune microenvironment and reducing T-cell depletion. Understanding the complex interplay between liver metastasis and immunotherapy response is crucial for optimising patient care in GC.

Key Words: Immunotherapy; Liver metastasis; Immune tolerance; Gastric carcinoma; Hepatic Siphoning

Core Tip: Liver metastasis affects the systemic immune response, reducing the efficacy of immunotherapy for gastric cancer patients with liver metastases. According to studies, the presence of liver metastases reduces the effectiveness of immunotherapy by lowering progression-free survival and objective response rates. Strategies such as liver-mediated radiation may aid in improving treatment outcomes. Understanding the intricate interplay between the two is crucial for offering the best possible treatment for stomach cancer with liver metastases.

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INTRODUCTION

This editorial comments on the article by Liu *et al*[1]. Gastric cancer (GC) ranks as the fifth most prevalent cancer globally and stands as the fourth principal contributor to cancer-related deaths worldwide[2]. Liver serves as the principal site for metastasis in GC[3]. In cases of GC accompanied by liver metastasis, the initial treatment typically involves a combination of fluoropyrimidines and platinum-based chemotherapy. Despite these efforts, the overall prognosis for patients in this situation continues to be unfavorable[4]. Thus, finding novel therapeutics for treating advanced GC represents an essential area of research.

DISCUSSION

Immunotherapy or immune checkpoint inhibitors, such as monoclonal antibodies against programmed cell death-1 or programmed cell death ligand-1 (PD-L1), have recently been demonstrated in numerous phase I and phase II trials to showcase a promising activity by restoring effective antitumor T-cell response within the tumor microenvironment and have improved overall survival for various cancers, including GC[5,6]. The efficacy of immunotherapy is linked to tumor-infiltrating lymphocytes and the expression of PD-L1 in tumors, with both subsequently serving as predictive factors[7]. Due to tissue-specific immunoregulation, the types of tumor-infiltrating lymphocytes differ across metastatic organ sites. Consequently, the response to immunotherapy varies at each metastatic site, influenced by the unique tumor-immune microenvironment[8].

Since the liver is an immunological organ and research has demonstrated hepatic immune tolerance, it is likely that liver metastases affect the effectiveness of immunotherapy by changing systemic anticancer activity, which includes the control of CD8+ and CD4+ T-cells[9]. Regarding the mechanism, new studies on mice have demonstrated that liver metastases cause antigen-specific T-cell death, eliminating activated CD8+ T-cells from the systemic circulation[10]. These results suggest that liver metastases may cause a depletion of T-cells throughout the body and might reduce the efficacy of immunotherapy[11]. Furthermore, inadequate activation of CD4+ T-cells, partial activation of CD8+ T-cells, and activation of regulatory T-cells are among the other pathways of liver-induced systemic immunological tolerance that have been documented[12].

CONCLUSION

According to recent studies, liver metastasis is a predictor of systemic advancement, tumor objective response rate and progression-free survival rate following immunotherapy, with those parameters being poorer in patients with GC and liver metastasis and vice versa[13]. Therefore, the existence of liver metastases may constitute a baseline risk that compromises the immunotherapy's effectiveness. Managing liver metastases by various means might improve the effectiveness of immunotherapy; in particular, hepatocellular siphoning of T-cells is decreased, and the immunological milieu of the liver is reshaped by liver-mediated radiotherapy[13].

FOOTNOTES

Author contributions: Chalkoo M, Bhat MY, and Wani YH designed the study; Bhat MY performed the research and typing; Wani YH performed the typing and editing the manuscript as well as analyzed the data; All authors have read and approved the final manuscript.

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