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EDITORIAL

Pembrolizumab in patients with gastric cancer and liver metastases: A paradigm shift in immunotherapy

Grigorios Christodoulidis, Dimitra Bartzi, Konstantinos Eleftherios Koumarelas, Marina Nektaria Kouliou

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Abstract

In this editorial, we explore the impact of immunotherapy and its safety in patients with advanced gastric cancer (GC) and liver involvement. GC, a formidable adversary in the oncology landscape, presents its most challenging battlefront when it reaches stage IV, often characterized by liver metastases. The prognosis for patients at this advanced stage is daunting, with systemic chemotherapy traditionally offering a median overall survival slightly over a year. However, the landscape of treatment is evolving, with new strategies and therapies offering a glimmer of hope.

Key Words: Gastric cancer; Immunotherapy; Pembrolizumab; Liver metastasis; Prognosis; Treatment

Core Tip: Given the multifaceted challenges of treating gastric cancer with liver metastases, adopting a personalized approach to therapy is crucial. This involves integrating biomarker testing, such as programmed cell death ligand 1 expression, into treatment decisions to identify likely responders to immunotherapy such as pembrolizumab. By tailoring treatment strategies based on individual patient characteristics and disease biology, clinicians can optimize therapeutic efficacy and mitigate potential adverse events, ultimately improving outcomes for patients navigating this complex clinical scenario.

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INTRODUCTION

Gastric cancer (GC) remains a significant global health challenge. GC is the fourth most common malignancy and the third leading cause of cancer-related deaths worldwide[1,2]. Approximately 2.0% to 9.9% of GC patients develop synchronous liver metastases, while up to 37% develop liver metastases metachronously following radical gastrectomy. Interestingly, almost 80% of metachronous liver metastases appear within the first 2 years after hepatic surgical treatment [3,4]. With over one million new cases in 2020 and an estimated 769000 deaths, it ranks fifth in incidence and fourth in mortality globally[1]. GC is the fourth most common cancer worldwide, accounting for approximately 5.7% of all cancer cases. The incidence of GC varies by geographic location, with higher rates observed in Eastern Asia (*e.g.*, Japan, Korea and China) and lower rates in Western countries. Liver metastases occur in a subset of GC patients, either synchronously (at the time of initial diagnosis) or metachronously (after primary treatment)[5]. GC presents a multifaceted landscape of risk factors, with chronic *Helicobacter pylori* infection as a prominent contributor alongside dietary habits such as high consumption of salted, smoked, or pickled foods, as well as tobacco and alcohol use. Genetic predisposition, particularly a family history of GC, and the presence of chronic atrophic gastritis further compound the susceptibility to this malignancy. Liver metastases, a significant complication, are often associated with advanced tumor stage, lymph node involvement, and aggressive tumor biology. Clinical presentation manifests with nonspecific symptoms including abdominal pain, weight loss, early satiety, and anemia, while liver metastases may introduce additional indicators like jaundice, hepatomegaly, and ascites. Prognosis for GC with liver metastases remains bleak, typically characterized by a median survival measured in months. Treatment modalities encompass systemic chemotherapy for symptom control and survival extension, surgical resection of liver metastases in select cases, and local therapies such as radiofrequency ablation, transarterial chemoembolization, and selective internal radiation therapy. Targeted therapies aimed at specific molecular pathways and immunotherapy are also emerging as potential options. Research endeavors are actively exploring novel therapeutic targets, refining patient selection criteria, advancing early detection strategies, and delving into personalized medicine approaches, all with the goal of improving outcomes in the management of GC and liver metastases[5]. In this editorial, we comment on the retrospective review by Liu *et al*[2] "Analysis of the impact of immunotherapy efficacy and safety in patients with gastric cancer and liver metastasis".

IMMUNOTHERAPY AND GC

Immune checkpoint inhibitors (ICIs) have transformed cancer therapy by augmenting the immune system's ability to combat tumor cells, targeting proteins like programmed cell death protein 1 and programmed cell death ligand 1 (PD-L1) to enhance immune recognition and attack cancerous cells. However, the response to ICIs exhibits heterogeneity across metastatic sites, with liver metastasis presenting distinct challenges. Understanding progression patterns and survival outcomes in response to ICIs is critical for refining patient care[6,7]. In retrospective studies involving GC patients treated with ICIs, two progression patterns emerged: Non-systemic progression, characterized by localized disease progression and improved overall survival (OS), particularly in the absence of liver metastasis[2], and systemic progression, associated with widespread metastasis and shorter survival times, notably influenced by liver metastasis[6]. Intratumoral immune cell density, particularly $CD8^+$ T-cells, was found to be lower in patients with liver metastasis after ICIs, while other immune cells showed no significant differences. Clinical implications include personalized approaches through biomarker testing to identify likely responders based on PD-L1 expression and other markers, tailored therapy selection, and patient education to ensure informed decisions and realistic expectations[6]. Additionally, considerations for maintaining quality of life alongside survival benefits are paramount, emphasizing the importance of balancing treatment efficacy with potential toxicities. Despite challenges, immunotherapy has promise for GC patients with liver metastasis, and through comprehensive understanding of progression patterns, refined treatment strategies, and holistic patient support, improved outcomes can be achieved[6-10].

NAVIGATING PEMBROLIZUMAB EFFICACY AND SURVIVAL

The KEYNOTE series of trials, notably KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062, have been pivotal in assessing the efficacy of pembrolizumab in GC, particularly in patients with a PD-L1 combined positive score (CPS) ≥ 10[11]. In third-line or later settings, KEYNOTE-059 demonstrated pembrolizumab's OS of 8 months and an objective response rate (ORR) of 17%, while KEYNOTE-061 in the second-line setting exhibited a median OS of 10 months with an ORR of 25%[11]. Notably, KEYNOTE-062 in the first-line setting reported a median OS of 17 months for pembrolizumab *vs* 11 months for chemotherapy, underlining its clinically meaningful survival benefit[1]. The United States Food and Drug Administration approval for pembrolizumab in combination with chemotherapy for HER2-negative gastric or gastroesophageal junction cancer was based on significant improvements in OS, progression-free survival, and ORR. The pivotal trial, KEYNOTE-859, showed improved OS (12.9 months *vs* 11.5 months) and ORR (51% *vs* 42%) with pembrolizumab *vs* placebo, with subgroup analysis revealing enhanced outcomes in patients with higher PD-L1 expression[12-15]. Real-world evidence supports pembrolizumab's feasibility in pre-treated patients, although its efficacy varies based on individual factors such as CPS score, necessitating a personalized approach, especially in the complex landscape of stage IV GC with liver metastasis[14,15]. Pembrolizumab's favorable benefit-to-risk profile is counterbalanced by immune-related adverse events, including dermatologic, gastrointestinal, hepatic, endocrine, and pulmonary complications, mandating a multidisciplinary approach for management[16]. Pembrolizumab treatment can trigger various adverse reactions, with dermatologic issues such as rash and pruritus being common, although manageable with topical treatments. Gastrointestinal problems such as colitis and diarrhea may arise, requiring immediate medical attention to prevent severe dehydration and electrolyte imbalances. Monitoring liver function is essential due to the potential risk of pembrolizumab-induced hepatitis, which can lead to severe liver injury if not addressed promptly. Endocrinopathies, including thyroid dysfunction and adrenal insufficiency, may necessitate hormone replacement therapy for management. Additionally, while rare, pneumonitis poses a serious concern, requiring prompt treatment to avoid significant morbidity. This extensive body of evidence underscores the transformative potential of pembrolizumab in GC treatment and the importance of tailored strategies to optimize patient outcomes in this challenging clinical setting. The efficacy of pembrolizumab in GC with liver metastases is a subject of ongoing research. While the response rates in clinical trials are modest, they represent a significant improvement over historical outcomes with chemotherapy alone. The potential for pembrolizumab to provide durable responses in a subset of patients is particularly encouraging[16].

CONCLUSION

The combination of epirubicin and cyclophosphamide with pembrolizumab has carved out a niche in the treatment landscape of GC with liver metastases. However, the safety and management of its associated complications are paramount. Its ability to improve survival outcomes and the quality of life for patients is a testament to the progress being made in the field of oncology. As research continues, there is hope that pembrolizumab will become an integral part of the treatment regimen for these patients, offering them a chance at a longer and better life. The response to immunotherapy in GC patients with liver metastasis was lower than in those without liver metastases[2]. This editorial provides a snapshot of the current understanding of pembrolizumab's safety and complications in the context of GC with liver metastasis. It synthesizes information from clinical trials and real-world studies to provide an overview of pembrolizumab's efficacy in GC with liver metastases. Clinicians must weigh the benefits of pembrolizumab against its potential risks and tailor their approach to each patient's unique clinical scenario. For a more comprehensive analysis, further reading and consultation of clinical trial publications are recommended.

FOOTNOTES

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