Clinical Oncology: Case Reports

Perspective

A SCITECHNOL JOURNAL

Gastric Adenocarcinoma Management: A Perspective

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Abstract

Gastric Adeno Carcinoma (GAC) remains a formidable global health challenge, marked by its geographical variability and the pressing need for improved therapeutic strategies. This opinion piece aims to delve into recent strides made in GAC management, with a specific focus on the localized and metastatic settings. We explore the details of adjunctive therapy for localized GAC and discuss the promising developments, including immune checkpoint inhibitors, for Microsatellite Instability High (MSI-H) GAC. In the metastatic arena, we survey the evolving realm of targeted therapies and immune checkpoint inhibitors, highlighting the recent approval of trastuzumab deruxtecan for HER-2-positive GAC. We also contemplate the prospects of claudin 18.2 (CLDN18.2) and Fibroblast Growth Factor Receptor (FGFR) as novel therapeutic targets in GAC.

Keywords: Gastric Adenocarcinoma; Immune checkpoint therapy; HER-2, targeted therapy; CLDN18.2; FGFR

Introduction

In 2023, the United States is expected to witness approximately 26,500 new cases of stomach cancer, affecting 15,930 men and 10,570 women [1]. On a global scale, stomach cancer emerged as the fifth most frequently diagnosed cancer in 2020, with an estimated 1,089,103 cases worldwide, and on a worldwide scale, it stands as the fourth most common cause of cancer-related mortality [1]. These statistics underscore the profound impact of stomach cancer and its continued relevance in the realm of global health. Gastric Adeno Carcinoma (GAC) is no exception, persisting as a significant challenge that spans across regions. Factors such as familial risk, dietary patterns, and environmental exposures play intricate roles in the epidemiology of this disease. Recent breakthroughs, notably the categorization of GAC into subtypes based on molecular pathways, particularly Microsatellite Instability-High (MSI-H), have initiated a transformative era in GAC management [2]. This article offers a comprehensive overview of the current state of GAC management, addressing the complexities encountered in treating localized GAC and highlighting the promising advancements in the management of metastatic cases.Tackling Localized GAC: An Intricate Quandary Localized GAC mandates surgical resection as the cornerstone of therapy, supplemented by adjunctive treatments like perioperative chemotherapy, postoperative adjuvant chemotherapy, or postoperative chemoradiation [3]. However, the absence of a universally endorsed approach for adjunctive therapy remains a substantial challenge. Several clinical trials, including Intergroup 116, MAGIC, ACTS-GC, FLOT-AIO, and CLASSIC, have contributed to the delineation of these approaches [4]. However, the persistent issue of incomplete postoperative therapy warrants the consideration of high-volume centers and multidisciplinary conferences to optimize localized GAC management. Engaging in clinical trials is a fundamental component of advancing outcomes, and a more comprehensive understanding of the molecular diversity within GAC is imperative.

A distinctive subset of patients with localized GAC bearing MSI-H/dMMR, constituting approximately 15% of cases, has come to light [5]. Immune checkpoint therapy, particularly Programmed Death-1 (PD-1) blockade, has demonstrated remarkable efficacy in this cohort, akin to its success in MSI-H/dMMR colorectal cancer. Recent trials have reported outstanding results, opening the door to the exploration of non-operative approaches for select MSI-H/dMMR GAC patients [5,6].

Advancements in Metastatic GAC Therapy: Targeted Therapies and Immune Checkpoints Metastatic GAC predominantly presents in Western countries, often diagnosed at advanced stages due to the lack of efficient screening protocols. Historically, the treatment landscape has revolved around combination chemotherapy regimens. Trastuzumab, an anti-HER-2 agent, was an initial breakthrough, followed by the approval of ramucirumab, an anti Vascular Endothelial Growth Factor receptor (VEGF) agent, in the second-line setting [7].

The advent of immune checkpoint inhibitors has introduced a new paradigm in metastatic GAC treatment. Phase 3 trials for nivolumab, pembrolizumab, and sintilimab have generated varying results, necessitating further clarity on upfront immune checkpoint therapy [8]. Notably, CHECKMATE 649 demonstrated improved survival with nivolumab in patients

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Received: October 10, 2023; Manuscript No: COCR-23-122284 **Editor Assigned:** October 14, 2023; PreQC Id: COCR-23-122284 (PQ) **Reviewed:** October 19, 2023; QC No: COCR-23-122284 (Q) **Revised:** October 23, 2023; Manuscript No: COCR-23-122284 (R) **Published:** October 27, 2023; DOI: 10.4172/cocr.6(10).316

with a Combined Positive Score (CPS) of at least 5 [9]. KEYNOTE-811 showed benefits with pembrolizumab plus trastuzumab in HER-2-positive patients [10]. These approvals have reshaped the treatment approach for GAC.

HER-2-Positive GAC: Expanding Treatment Options

The HER-2-positive GAC subset has seen substantial progress with the approval of trastuzumab deruxtecan, an Antibody-Drug Conjugate (ADC) combining trastuzumab and a topoisomerase inhibitor [11]. Promising results from DESTINY-Gastric01 and DESTINY-Gastric02 have reinforced the potential of this agent, with ongoing phase 3 evaluation via the DESTINY-Gastric04 trial [11]. Additionally, various other HER-2-directed therapies, such as ZW25, margetuximab, and bispecific HER-2 monoclonal antibodies, are being explored, offering renewed hope for the management of HER-2-positive GAC [12].

Claudin 18.2 (CLDN18.2) and Fibroblast Growth Factor Receptor (FGFR): Emerging Targets

Zolbetuximab, a CLDN18.2 monoclonal antibody, has demonstrated potential in GAC, both as monotherapy and in combination with triplet chemotherapy [13]. Ongoing phase 3 trials, including SPOTLIGHT and GLOW, will shed further light on its clinical utility [14]. FGFR has also emerged as a noteworthy target in GAC, with bemarituzumab showing improved overall survival [15]. The FORTITUDE-101 study is currently evaluating this combination, with multiple other FGFR agents undergoing exploration, offering diverse therapeutic options [16].

Conclusion

Gastric adenocarcinoma remains a formidable global health challenge, characterized by regional disparities and influenced by various factors such as familial risks, dietary habits, and environmental exposures. However, the recent advances in our understanding of the disease, including the categorization of GAC into molecular subtypes like MSI-H, have ushered in a promising new era in its management. The intricacies of treating localized GAC have prompted the exploration of non-operative approaches for specific patient subgroups. Meanwhile, the advent of immune checkpoint inhibitors and the emergence of innovative therapies like trastuzumabderuxtecan are reshaping the landscape of metastatic GAC treatment. Emerging targets such as Claudin 18.2 (CLDN18.2) and Fibroblast Growth Factor Receptor (FGFR) offer renewed hope. As we continue to navigate this evolving terrain, the future of gastric adenocarcinoma management appears increasingly hopeful, with a focus on advancing patient outcomes and improving overall quality of life.

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