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EDITORIAL

Revolutionizing gastric cancer treatment: The potential of immunotherapy

Grigorios Christodoulidis, Konstantinos Eleftherios Koumarelas, Marina Nektaria Kouliou

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Grigorios Christodoulidis, Konstantinos Eleftherios Koumarelas, Marina Nektaria Kouliou, Department of General Surgery, University Hospital of Larissa, Larissa 41110, Greece

Corresponding author: Grigorios Christodoulidis, MD, PhD, Surgeon, Department of General Surgery, University Hospital of Larissa, Mezourlo, Larissa 41110, Greece. gregsurg@yahoo.gr

Abstract

Gastric cancer, a prevalent malignancy worldwide, ranks sixth in terms of frequency and third in fatality, causing over a million new cases and 769000 annual deaths. Predominant in Eastern Europe and Eastern Asia, risk factors include family medical history, dietary habits, tobacco use, *Helicobacter pylori*, and Epstein-Barr virus infections. Unfortunately, gastric cancer is often diagnosed at an advanced stage, leading to a grim prognosis, with a 5-year overall survival rate below 5%. Surgical intervention, particularly with D2 Lymphadenectomy, is the mainstay for early-stage cases but offers limited success. For advanced cases, the National Comprehensive Cancer Network recommends chemotherapy, radiation, and targeted therapy. Emerging immunotherapy presents promise, especially for unresectable or metastatic cases, with strategies like immune checkpoint inhibitors, tumor vaccines, adoptive immunotherapy, and nonspecific immunomodulators. In this Editorial, with regards to the article "Advances and key focus areas in gastric cancer immunotherapy: A comprehensive scientometric and clinical trial review", we address the advances in the field of immunotherapy in gastric cancer and its future prospects.

Key Words: Immunotherapy; Adaptive immunotherapy; Tumor vaccines; Chimeric antigen receptor therapy; Tumor-infiltrating lymphocytes therapy; Natural killer therapy; Cytokine-induced killer therapy; Engineered T cell receptor therapy; Immune checkpoint inhibitors

Core Tip: Immunotherapy, especially immune checkpoint inhibitors (ICIs), has revolutionized cancer treatment by targeting programmed cell death 1, programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), enhancing the immune response. While PD-L1 and CTLA-4's prognostic significance in gastric cancer remains debatable, ICIs like nivolumab and pembrolizumab show promise. Tailored approaches, such as zolbetuximab for CLDN 18.2 or trastuzumab, pembrolizumab, and chemotherapy for human epidermal growth factor receptor 2-positive cases, demonstrate effectiveness. Tumor vaccines and dendritic cell-based vaccines hold potential in personalized therapy. Adoptive Immunotherapy utilizes tumor-infiltrating lymphocytes therapy, engineered T cell receptor therapy, Chimeric antigen receptor T-cell therapy, natural killer cell therapy, and cytokine-induced killer cell therapy, each with distinct benefits and challenges. The immunotherapy landscape continues to evolve, offering hope for improved cancer management.

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INTRODUCTION

Gastric cancer ranks among the most prevalent malignancies worldwide, occupying the sixth position in terms of frequency and the third spot in terms of fatality, accounting for over one million new cases and 769000 annual deaths[1-3]. It is primarily observed in Eastern Europe and Eastern Asia. Noteworthy risk factors include family medical history, dietary practices, tobacco use, *Helicobacter pylori* and Epstein-Barr virus (EBV) infections. Regrettably, the diagnosis of gastric cancer is often delayed, with more than half of patients being diagnosed at the stage of advanced metastatic cancer, leading to a significantly unfavorable prognosis. The 5-year overall survival (OS) rate in such cases remains below 5%, and the life expectancy is limited to merely 8 months[1,2].

Up to this point, surgical intervention remains the sole definitive treatment for early-stage gastric cancer when coupled with a D2 Lymphadenectomy. Nevertheless, even with this approach, the 5-year OS rate does not exceed 50%[4]. For advanced gastric cancer, the recommended management according to the National Comprehensive Cancer Network (NCCN) involves the use of double or triple platinum and fluoropyrimidine-based chemotherapy, combined with radiation therapy and targeted therapy[2].

In recent years, emerging immunotherapy has exhibited promising outcomes, particularly for patients with unresectable, locally advanced, recurrent, or metastatic gastric cancer. There are four principal strategies in immunotherapy: Immune checkpoint inhibitors (ICIs), tumor vaccines, adoptive immunotherapy (ACT), and nonspecific immunomodulators[1,5]. Targeted therapies function by inhibiting cell growth through the blockade of specific molecular pathways and proteins, while immunotherapy stimulates the patient's immune response against cancerous cells. However, owing to the diverse molecular subtypes of gastric cancer and the intricate nature of the tumor microenvironment, immunotherapy proves effective only within specific patient subgroups[1,5]. For human epidermal growth factor receptor 2 (HER2)-positive gastric cancer, tailored regimens encompassing Trastuzumab, Pembrolizumab, and XELOX/PF are employed, while for HER2-negative cases, first-line chemotherapy is combined with nivolumab, cindilimab, or tislelizumab[1,2].

IMMUNOTHERAPEUTIC STRATEGIES

The most commonly employed form of immunotherapy among the various alternatives is ICIs. The introduction of inhibitors targeting programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) has profoundly transformed the landscape of cancer management. The interaction between PD-L1 and PD-1 induces T-cell dysfunction, exhaustion, and an elevation in their tolerance levels[1,5]. Consequently, the inhibition of PD-1 and PD-L1, as well as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), serves to augment the immune response and activate T-cells. Despite the application of immunotherapy, there exist conflicting findings concerning the prognostic implications of PD-L1 or CTLA-4 positivity in gastric cancer[1,4]. ICIs are currently in clinical use and are undergoing extensive research due to their demonstrated lower toxicity, improved tolerability, and potential for yielding superior outcomes when compared to conventional chemotherapy. Nowadays the effectiveness of a PD-L1 inhibitor can be foreseen. The assessment of MSI status, PD-L1 and PD-1 expression levels as well as the EBV status gives insight for the success rate of ICIs utilization. EBV positive tumors, MSI-H tumors, as well as tumors with increased expression of PD-L1 or PD-1 in tumor cells and infiltrating immune cells have a significant better response to ICIs[6]. In a meta-analysis conducted by Liu *et al*[2], various ICIs were evaluated for their efficacy and safety. Nivolumab, pembrolizumab, rilotumumab, Andecaliximab (ADX), and bevacizumab were associated with superior progression-free survival (PFS), while pembrolizumab and nivolumab exhibited improved OS when contrasted with traditional chemotherapy[2]. It is worth noting that these results did not achieve statistical significance. In contrast, nimotuzumab and ipataserib demonstrated less favorable outcomes in terms of both PFS and OS in comparison to chemotherapy. Bavacizumab and ADX were found to be safer and associated with more manageable complications than chemotherapy. Through a subgroup analysis focusing on different types of gastric

cancers, Liu *et al*[2] proposed several regimens deemed most effective:

For patients with CLDN 18.2, the combination of zolbetuximab with chemotherapy led to increased OS and PFS. In HER2-negative cases, the most effective regimen was found to be nivolumab in conjunction with chemotherapy, as suggested by the findings of the Checkmate-649 study. For individuals with HER2-positive gastric cancer, especially those who are untreated, unresectable, or have metastatic disease, the simultaneous use of trastuzumab, pembrolizumab, and chemotherapy emerged as the most effective approach, supported by the NCCN guidelines. In cases of MET-1 positive gastric cancer, no immunotherapy regimen was found to confer significant benefits. Lastly, as a second-line treatment for advanced gastric cancer, the utilization of vamucirumab and paclitaxel was proposed[2].

An additional category of immunotherapy involves the utilization of tumor vaccines. There are 4 types of tumor vaccines: cell-based, protein- or peptide-based, or gene-based (DNA/RNA), predominantly relying on dendritic cells (DCs) as their primary adjuvants. DCs are acknowledged as antigen-presenting cells (APCs) that, through the processing and presentation of antigens to T-cells, evoke and regulate the adaptive immune response in patients. Consequently, the employment of DCs as an immunotherapeutic measure holds the potential to activate and modulate an anti-tumor immune response[1,7]. Notably, DCs vaccines are designed to exclusively target tumor neoantigens, thereby instigating a personalized approach that has demonstrated the capability to induce complete tumor regression, as evidenced in clinical trials, rendering them a prominent subject of contemporary research[1,8]. DCs fused with gastric cancer cells or carrying peptides and RNAs may stimulate effectively the patients immune response. Right now 20 out of 23 trials on tumor vaccines, concern DCs vaccines. M-RNA vaccines are a great alternative, with increased efficacy and a rapid immune response. These vaccines when combined with chemotherapies based on cisplatin and 5-fluorouracil on clinical trials give encouraging results[5]. Nevertheless, the domain of gastric cancer presents a formidable challenge due to increased immunogenicity, antigenic shifts, and immune evasion when attempting to target tumor antigens. The immune system's evasion is principally attributed to the fact that these neoantigens are typically present in other tissues, consequently eluding recognition by APCs[1,7]. According to a bibliometric analysis conducted by Li *et al*[1], there have been 23 clinical trials aimed at elucidating the efficacy of tumor vaccines[1].

One of the most pivotal forms of immunotherapy is ACT. The fundamental concept underlying this technique is to transfer lymphocytes and other immune cells with the purpose of fortifying the anti-tumor response, generating effector T-cells that specifically target tumor antigens, and enhancing the function of regulatory T-cells, ultimately leading to improved outcomes and prognosis[1]. Physicians have at their disposal five distinct types of adaptive immunotherapy:

Tumor-infiltrating lymphocytes (TIL) therapy, which harnesses immune cells from within the tumor, enabling improved recognition of tumor antigens, heightened specificity, and reduced toxicity. The assessment of TIL serves as a valuable biomarker, and the coexistence of PD-1-positive and TIL-positive entities in gastric cancer correlates with superior outcomes in terms of PFS and OS[1,5].

Engineered T cell receptor (TCR) therapy, which operates by presenting antigens with specific Major Histocompatibility Complex (MHC) molecules, resulting in effective tumor regression. However, the use of high-avidity TCRs may give rise to significant toxicity[1,5].

Chimeric antigen receptor T-cell (CAR-T) therapy, sharing a similar principle, employs genetically engineered T cells capable of recognizing tumor antigens independently of MHC molecules. The fourth generation of CAR-T therapy circumvents immunosuppression and mitigates toxicity. Common targets include mesothelin, ANTXR1, MUC3A, and CLDN 18.2, with the latter being a subject of ongoing clinical trials[1,5,9].

Natural killer (NK) cell therapy, the fourth category of immunotherapy, leverages the potential of increased numbers of functional NK cells to enhance patient outcomes. In patients with gastric cancer, NK cells often exhibit an elevated expression of PD-1, exacerbating the prognosis. In animal models, the simultaneous use of interleukin-2 activated NK cells with anti-PD-1 treatment has been shown to impede tumor growth and facilitate immune cell infiltration into the tumor. However, NK cell therapy necessitates substantial quantities of effective NK cells, limiting its applicability[1,5,10].

Lastly, cytokine-induced killer cells represent a viable alternative, combining the cytotoxic and anti-tumor capabilities of CD3+CD56- T cell and CD3+CD56+ T-lymphocytes while operating without the constraints of MHC molecules[1,5].

CONCLUSION

Since the development of the ICIs, the field of immunotherapy is advancing with significant rates. Many novel approaches are under extended research and in clinical trials in order to assess the efficacy of each therapy and the toxicity deriving from their use. Nowadays the use of immunotherapy tends to integrate more and more in order to achieve precision medicine and the detection of novel biomarkers will assist to a better tailored and personalized use of these therapies.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Grigorios Christodoulidis 0000-0003-3413-0666; Konstantinos Eleftherios Koumarelas 0000-0002-5614-4770; Marina Nektaria Kouliou 0000-0002-2055-2297.

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