

PD-1 Blockade in the Treatment of Gastric Cancer

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Abstract

Gastric cancer is the fifth most common malignancy in the world and the third with most deaths. This makes these tumours of the utmost importance, especially regarding the treatment of patients with these malignancies. The current therapies include endoscopic resection, surgery and chemotherapy. However, the high mortality rate observed in these tumours calls for new and more personalized therapies, with immunotherapy having an important role in the treatment of these patients.

In fact, several studies have shown the benefit of blocking immune checkpoints such as PD-1 using drugs like pembrolizumab and nivolumab, in the treatment of patients with gastric cancer. The use of these drugs had good outcomes regarding ORR, PFS and OS, while also being associated with tolerable side effects.

This review aims to elucidate on the emerging role of PD-1 blockade in the treatment of gastric cancer.

Keywords: Gastric Cancer; Immunotherapy; Nivolumab; PD-1; Pembrolizumab

Abbreviations

CPS: Combined Positive Score; DOR: Duration of Response; HER-2: Human Epidermal Growth Factor Receptor 2; MSI: Microsatellite Instability; OGJ: Oesophageal Gastric Junction; ORR: Overall Response Rate; OS: Overall Survival; PD-1: Programmed Cell-Death 1; PD-L1: Programmed Death-Ligand 1; PFS: Progression Free Survival; TME: Tumour Microenvironment

Introduction

Gastric cancer is the 5th most commonly diagnosed malignancy worldwide, while being responsible for around 8% of all cancer-related deaths in the world [1], mostly due to the late diagnosis [2].

In fact, the poorer prognosis usually associated with gastric cancer might relate to the inherent aggressive biology of these tumours and the fact that the available therapies are not the most effective [3], granting the need for new treatment options for these patients.

The current treatment options for gastric cancer include endoscopic resection (for earlier stages), surgery with lymphadenectomy in surgically resectable tumours, chemotherapy schemes starting with platinum and fluoropyrimidine combinations, as well as targeted therapies like trastuzumab (anti-HER2), ramucirumab (anti-angiogenic) and nivolumab or pembrolizumab (anti-PD-1), with the latter most commonly used in advanced stages [2].

Indeed, immunotherapy has now a role in the treatment of chemorefractory gastric cancer, mostly in tumours with MSI [3]. This review aims to elucidate the promising role of PD-1 blockade in the treatment of patients with gastric cancer.

Methods

A PubMed search was done in April 2021, using the query "[gastric cancer OR gastric tumour OR gastric neoplasia] AND (pembrolizumab OR nivolumab) AND (PD-1 OR anti-PD1 OR anti-PD-1)". Upon selection of articles based on the referred query, a total of 8 articles were included in this mini-review.

Gastric cancer

The main risk factors associated with the development of gastric cancer include advanced age, dietary factors such as high salt intake and low fruit and vegetables consumption, *Helicobacter pylori* infection, active smoking, gastroesophageal reflux disease and high alcohol intake [1,2].

On the other hand, gastric cancer is characterized by a late and non-specific symptomatic presentation, with most patients presenting with advanced disease at diagnosis [2]. In fact, patients tend to present with dyspepsia, anorexia or early satiety, weight loss, abdominal pain and dysphagia (in proximal tumours) [2].

At first, gastric tumours were classified based on the epithelial histological appearance. However, other characteristics have been described as more important when it comes the prognosis of these tumours, with the most relevant ones related to the TME, such as TILs and tumour-stroma ratio [2,4].

On the other hand, there are four distinct molecular subtypes of gastric cancer: Epstein-Barr Virus positive, microsatellite instable, genomically stable and chromosomal unstable, which lead to the possibility of different treatment options based on the tumoural molecular pattern [5].

In fact, gastric adenocarcinoma is characterized by a robust inflammatory TME with a high rate of TILs, which are, in turn, responsible for the host's anti-tumour response and are currently seen as a prognosis factor [6]. However, tumour cells are capable of evading the host's immune system through several mechanisms, with the overexpression of immune checkpoints as one of them. Indeed, some tumours overexpress checkpoints like PD-L1, making the blockade of the PD-1/PD-L1 axis a great therapeutic option in these patients [3].

Immunotherapy in gastric cancer

PD-1 is expressed on activated T cells and other immune cells and interacts with PD-L1 and PD-L2 (present on antigen presenting cells, for example) in order to downregulate the immune system resulting in an exhaustion of effector T cells, a known mechanism to avoid an excessive inflammatory response and auto-immune diseases. However, cancer cells take advantage of this mechanism by overexpressing this immune checkpoint allowing the tumour to evade the host immune reaction [3].

This immune-evasion is the rationale for the blockade of immune checkpoints such as PD-1 in the treatment of cancer, as it allows the immune system to recognize the tumour and subsequently enrol in an anti-tumoural response [3].

In fact, there have been several studies showing the benefit of treating gastric tumours with PD-1 blockers, especially those with a high CPS (a score accounting for the number of PD-L1 positive tumour and immune cells) [3].

Some studies have been done in order to evaluate the advantages of PD-1 blockade in the treatment of gastric cancer, mostly in a second and third line setting [3].

KEYNOTE-062 was a study comparing pembrolizumab with or without chemotherapy and chemotherapy alone as a first line setting in patients with PD-L1 positive and HER2-negative advanced gastric adenocarcinoma. The median OS was 10.6 months comparing with 11.1 months in chemotherapy although with a better safety profile. However, upon selection of patients with a higher PD-L1 positivity, the OS was favourable for pembrolizumab (17.4 vs. 10.8 months) [3,7,8].

On the other hand, KEYNOTE-012 studied pembrolizumab in the treatment of patients with previously treated advanced gastric and OGJ adenocarcinoma, all PD-L1 positive. This showed an ORR of 22% with a median DOR of 40 weeks, median PFS of 1.9 months and OS of 11.4 months [3].

Another study, KEYNOTE-069 aimed to evaluate pembrolizumab in previously treated patients with gastric or OGJ adenocarcinoma, regardless of PD-L1 expression. This study showed an ORR of 15.5% in PD-L1 positive tumours and 6.4% in PD-L1 negative, highlighting the importance of PD-L1 expression in the selection of patients eligible for treatment with PD-1 blockers. These results were the fundamental for the approval of pembrolizumab in the treatment of PD-L1 positive gastric or OGJ adenocarcinoma that had progressed after previous therapies [3,8].

Accordingly, KEYNOTE-061 has also shown the benefit of PD-L1 expression in gastric tumours regarding the response to pembrolizumab. In this study, PD-L1 positive and MSI tumours showed the greatest benefit in pembrolizumab therapy while also having a beneficial safety profile [3].

Likewise, ATTRACTION-4 aimed to study chemotherapy with and without nivolumab in the treatment of HER-2 negative, advanced gastric or OGJ adenocarcinoma. In this study, radiological response rates were improved, as well as PFS (10.5 months adding nivolumab vs. 8.3 with chemotherapy alone). However, the OS was similar in both groups, perhaps due to patients changing from one study arm to the other [7].

Checkmate-649 was another study evaluating the treatment of advanced gastric adenocarcinoma with nivolumab plus chemotherapy as a first-line treatment versus chemotherapy alone. This study showed that in patients with a CPS > 5 the use of nivolumab showed advantage in radiological response, PFS and a 3 month gain in OS [7,8].

Furthermore, the use of PD-1 blockers such as pembrolizumab and nivolumab in the treatment of patients with gastric or OGJ cancer has shown great benefit not only in response rates and OS, but also regarding the more tolerable adverse events, with a low rate of high grade treatment related adverse events [7,8].

Indeed, these studies have granted the approval of pembrolizumab as monotherapy in a 3rd line therapy for gastric and OGJ adenocarcinoma expressing PD-L1 [8].

Study	Main study characteristics	Main Results
KEYNOTE-062 [3]	Comparison between pembrolizumab +/- chemotherapy and chemotherapy alone as a first line setting in patients with PD-L1 positive and HER2-negative advanced gastric adenocarcinoma.	Median OS: 10.6 months in all patients; 17.4 months in PD-L1 positive patients
KEYNOTE-012 [3]	Pembrolizumab in the treatment of patients with PD-L1 positive, previously treated, advanced gastric and OGJ adenocarcinoma	ORR: 22% Median DOR: 40 weeks PFS: 1.9 months OS: 11.4
KEYNOTE-069 [8]	Pembrolizumab in previously treated patients with gastric or OGJ adenocarcinoma, regardless of PD-L1 expression	ORR: 15.5% in PD-L1 positive tumours vs. 6.4% in PD-L1 negative tumours
KEYNOTE-061 [3]	Response to pembrolizumab in gastric tumours	Greatest benefit in PD-L1 and MSI positive tumours
ATTRACTION-4 [7]	Response to chemotherapy +/-nivolumab in the treatment of HER-2 negative, advanced gastric or OGJ adenocarcinoma.	PFS: 10.5 months vs 8.3 months (with and without the addition of nivolumab)
Checkmate-649 [7]	Treatment of advanced gastric adenocarcinoma with nivolumab plus chemotherapy as a first-line treatment vs. chemotherapy alone	Better results in radiological response and PFS 3 months gain in OS with addition of nivolumab

Table 1: Main studies and results regarding PD-1 blockade in the treatment of gastric and OGJ adenocarcinoma.

Discussion

Gastric cancer is known for its poor prognosis, partly due to the advanced stage on diagnosis, but also due to the poor response to the available treatment options. With the advances in science and better understanding of the TME, several therapeutic options have since emerged and are promising alternatives for these patients. In fact, studies have shown improvement in ORR, PFS and OS of patients with gastric cancer when treated with pembrolizumab or nivolumab. However, there is still a great need for more studies evaluating the outcomes of patients treated with anti-PD1, both regarding the tumoural response and safety profile, as well as long-term studies evaluating if the responses are durable enough. Furthermore, there is also a great need for studies regarding the advantages of PD-1 blockade when comparing with standard therapy options, namely in a first line setting, as well as evaluating which patients in specific benefit the most from these therapies.

Besides, these drugs have a steep price and there is a great need for cost-effectiveness studies, in order to evaluate the compatibility of using these drugs in a real life setting and not only in controlled studies.

Nonetheless, PD-1 blockade is a promising therapeutic option in patients with gastric and OGJ tumours and should be taken in account when treating these patients.

Conclusion

Gastric cancer is a common tumour worldwide and is associated with high morbidity and mortality rates, with the current available therapies not being effective enough in the treatment of these patients. With the advances in cancer treatment, new drugs have emerged, such as PD-1 blockers like pembrolizumab and nivolumab.

Despite the initial disbelief regarding the treatment of gastric cancer with these drugs, several studies have since shown the benefits of the incorporation of PD-1 blockade in the treatment of gastric cancer patients, especially in the second and third line setting.

Nonetheless, there is still need for studies evaluating the best type of tumours that benefit from these treatments, with those expressing PD-L1 being good candidates at the moment.

Conflict of Interest

There are no conflicts of interest to declare.

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