short review

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Dual immune checkpoint blockade in gastroesophageal tumors: never say never

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Summary Immunotherapy was proven to be effective as first-line treatment for a subgroup of patients with gastroesophageal tumors and is already established as the standard of care. However, chemotherapy remains the backbone of treatment in both advanced and resectable stages. Dual checkpoint inhibition produces synergistic activation of immune cells and enhanced antitumor activity, and could thus represent an alternative to chemotherapy. So far, there is evidence for the combination strategies of inhibitors of the PD-L1/PD-1 axis and CTLA4, LAG3 and TIGIT. A combination therapy of nivolumab+ipilimumab has already been approved as first-line treatment for patients with advanced esophageal squamous cell carcinoma. Evaluation of other concepts is ongoing. The aim of this review is to summarize current knowledge about dual inhibition of immune checkpoint inhibitors in the treatment of gastroesophageal carcinoma and to discuss the available evidence from a clinical perspective.

Keywords Gastroesophageal cancer · Squamous cell carcinoma · Immunotherapy · Dual immune checkpoint inhibition · High microsatellite instability

Introduction

The first attempts to establish chemotherapeutic agents were made in the early 1940s by Sidney Farber, who developed folate antagonists as agents for the treatment of hematological malignancies [1]. Following the modest success of this approach, several compounds were subsequently developed and tested in a variety of hematological and oncological diseases. Thus, as one of the first chemotherapeutic agents developed during this period [2], fluoropyrimidines became the backbone of the treatment of many oncological diseases, including colon cancer, pancreatic cancer, breast cancer and gastroesophageal cancer.

Interestingly, fluoropyrimidines still represent an important part of antitumor treatment of gastroesophageal carcinoma in both metastatic and resectable settings, and several attempts to establish targeted therapies have shown modest results [3, 4]. Therefore, the introduction of immunotherapy together with chemotherapy for the treatment of a subgroup of patients with metastatic gastroesophageal cancer was revolutionary and led to high expectations that even a chemotherapy-free regimen could be plausible [5–7], if different immunotherapy-inhibitory molecules are combined or the appropriate biomarker-driven subgroup of patients are identified.

To be implemented in clinical routine, dual immunotherapy combinations should show advantages over chemotherapy alone or chemotherapy plus single-agent immunotherapy in several directions: (i) manageable and acceptable toxicity profile; (ii) prolonging patient outcomes to a significant and relevant extent; (iii) acceptable financial toxicity in relation to the magnitude of the clinical benefit.

The aim of this review is to summarize current knowledge about dual inhibition of immune checkpoint inhibitors in the treatment of gastroesophageal tumors and to discuss the available evidence from a clinical perspective.

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Dual immune checkpoint inhibition in advanced gastroesophageal tumors

Inhibition of CTLA4 + PDL-1/PD-1 axis

Nivolumab+ipilimumab

Checkmate-32 was the first in class study assessing the combination treatment of nivolumab+ipilimumab in patients with chemotherapy-refractory gastroesophageal cancers [8]. A total of 160 patients were randomized into following three groups: nivolumab 3 mg/kg (n = 59), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n = 49), and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 52). Objective response rates (ORR) as primary endpoint were 12, 24, and 8% in the three groups, respectively. Responses were observed independent of tumor programmed death-ligand 1 (PD-L1) status. The 12-month overall survivals (OS) were 39, 35, and 24%, respectively. Treatment-related grade 3/4 treatment-related adverse events (TRAEs) were reported in 17, 47, and 27% of patients, respectively. Nivolumab and nivolumab+ipilimumab demonstrated clinically meaningful antitumor activity in this group of heavily pretreated patients, durable responses and encouraging long-term OS. However, there were some concerns regarding the safety profile in patients with combination treatment and higher ipilimumab doses. Nevertheless, this encouraged the research group to design further phase III studies evaluating nivolumab+ipilimumab in earlier lines of therapy for gastroesophageal cancers.

Checkmate-649 was a global, randomized, open-label phase III trial randomizing 2031 advanced, metastatic or unresectable human epidermal growth factor 2 (HER2)-negative gastroesophageal carcinoma patients as first-line treatment across the three groups: nivolumab+chemotherapy, chemotherapy alone, and nivolumab+ipilimumab (at 1 mg/kg q2w plus ipilimumab at 3 mg/kg q6w, as the second group in CheckMate-32 study) [6, 9]. Enrollment to the nivolumab+ipilimumab group was closed early due to increased adverse events per recommendation from the data monitoring committee; 409 patients were already randomized to nivolumab+ipilimumab at the time point of the study closure. Median OS was 11.2 months in nivolumab+ipilimumab arm versus 11.6 months in chemotherapy arm (HR 0.89; p = 0.2302) in patients with combined positive score (CPS) ≥ 5. 1-year OS rates were 47 and 48%, respectively. Progression-free survival (PFS) and ORR were not improved with nivolumab+ipilimumab versus chemotherapy in patients with CPS ≥ 5 or in all randomized patients. Grade 3/4 TRAEs occurred in 38 and 46% with nivolumab+ipilimumab versus chemotherapy, respectively.

As expected, nivolumab+ipilimumab showed longer median OS (unstratified HR 0.28) and higher ORR (70 versus 57%) compared with chemotherapy in patients with microsatellite instable (MSI-H) tumors.

CheckMate-648 study represented another large global, randomized, open label phase III trial testing dual immune checkpoint blockade as first-line treatment in patients with gastroesophageal tumors [5]. This study randomly assigned 970 patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) to following arms: nivolumab+chemotherapy, nivolumab+ipilimumab (3 mg/kg q2w and 1 mg/kg q6w, as the third group in CheckMate32 study), or chemotherapy. Patients with tumor cell PD-L1 expression (tumor proportion score, TPS) ≥ 1% (primary endpoint) had a highly statistically significant improvement in OS with nivolumab+ipilimumab arm versus chemotherapy alone; however, the numerical OS rates were lower than that observed in nivolumab+chemotherapy arm and there has been a cross-over of the survival curves after 6 months of treatment indicating rapid progressing patients under nivolumab+ipilimumab treatment (OS = 13.2 vs 10.7 months; HR = 0.64; p = 0.001). Based on these results, both nivolumab+chemotherapy and nivolumab+ipilimumab received approvals for the primary endpoint population of the study by Federal Drug Administration and European Medicines Agency.

In ESMO-GI 2022, factors associated with delayed onset of effect of nivolumab+ipilimumab vs nivolumab+chemotherapy or chemotherapy mono in ESCC patients were presented. According to this post hoc analysis, age (< 65 years), weight (< 60 kg), disease status at current diagnosis (de novo metastatic), baseline neutrophil/lymphocyte ratio (< 4), baseline tumor burden (≥ Q3), liver metastasis (yes), and alcohol use (never/unknown) were associated with enhanced benefit from nivolumab+ipilimumab [10]. Working group suggested that initial increased incidence of early death with nivolumab+ipilimumab did not preclude long-term benefit for the overall population. Furthermore, grade 3/4 TRAEs with potential immunologic etiology were observed in ≤ 6% of patients treated with nivolumab+ipilimumab across organ categories.

Tremelimumab + durvalumab

Another dual checkpoint inhibitor combination represents the combination of anti-CTLA4 inhibitor tremelimumab and anti-PD-L1 inhibitor durvalumab. This combination was tested in a randomized, multicenter, open-label, phase Ib/II study in patients with chemotherapy-refractory gastroesophageal cancer [11]. Second-line patients were randomized 2:2:1 to receive durvalumab+tremelimumab (arm A), or durvalumab (arm B) or tremelimumab monotherapy (arm C), and third-line patients received durvalumab+tremelimumab (arm D). ORRs (co-primary endpoint) were 7.4, 0, 8.3, and 4.0%, respectively. PFS rates (co-primary endpoint) at 6 months were 6.1, 0, 20, and 15%, respectively and 12-month OS rates

were 37.0, 4.6, 22.9, and 38.8%, respectively. Grade 3/4 TRAEs were reported in 17, 4, 42, and 16% of patients, respectively. Response rates were low regardless of monotherapy or combination strategies. No new safety signals were identified; however, combination treatment demonstrated higher grade 3/4 events.

Inhibition of PD-1 and LAG3

Lymphocyte activation gene 3 (LAG-3) is an immune checkpoint molecule that negatively regulates effector T-cell function and represents as a marker of T-cell exhaustion [12]. Currently, a phase III study in advanced melanoma demonstrated increased outcome of patients when treated with nivolumab+ anti-LAG-3 antibody relatlimab as first-line treatment [13]. CA224-060 study was a randomized, open-label, multicenter, phase 2 study of relatlimab+nivolumab with oxaliplatin-based chemotherapy vs nivolumab+oxaliplatin-based chemotherapy as first-line treatment in patients with advanced gastroesophageal tumors [14]. According to a recent entry in clinicaltrials.gov, the ORR (primary endpoint) was to be 48.5% in nivolumab+relatlimab+chemotherapy versus 61.2% in nivolumab+chemotherapy arm. Serious adverse events were observed in 78.7% of patients in nivolumab+relatlimab+chemotherapy arm with 60.3% all-cause deaths, whereas these were 69.6% versus 53.3% in nivolumab+chemotherapy arm, respectively. Further data are expected soon.

Inhibition of TIGIT and PD-1/PD-L1 axis

The current standard of care for patients with locally advanced, unresectable ESCC is definitive concurrent chemoradiotherapy (dCRT). However, ESCC has poor prognosis, with almost half of patients experiencing tumor recurrence after dCRT; thus, further therapy options are needed in this setting [15].

TIGIT is a novel inhibitory immune checkpoint present on activated T cells and natural killer cells in multiple cancers; TIGIT expression correlated with PD-1 especially in tumor infiltrating T cells [16]. Tiragolumab is a fully human IgG1/kappa anti-TIGIT monoclonal antibody. In the phase Ib GO30103 study, tiragolumab in combination with atezolizumab demonstrated promising antitumor activity in patients with heavily pretreated metastatic esophageal cancer independent of PD-L1 status or histology [17]. SKYSCRAPER-07 is a global, randomized, double blinded phase III study, which will determine whether tiragolumab+atezolizumab combination provides superior clinical benefit to atezolizumab monotherapy or placebo in patients with unresectable ESCC whose cancers have not progressed following dCRT. Recruitment is ongoing [18].

Ociperlimab is a novel, humanized, monoclonal antibody that targets TIGIT with high specificity and affinity, blocking the interaction with its ligands on tumor cells. AdvanTIG-203 is a second-line phase 2, global, randomized, double-blind, placebo-controlled study of patients with advanced ESCC, whose tumors express PD-L1. Patients will be randomized to either ociperlimab+tislelizumab (anti-PD-1 antibody), or tislelizumab+placebo [19].

Dual immune checkpoint inhibition in resectable gastroesophageal tumors

MSI-H is a useful marker for predicting response to immunotherapy in advanced cancer [20]. There is growing evidence that MSI-H is also a reliable marker for neoadjuvant treatment, as retrospective analysis of prospective large phase III studies suggested that patients with MSI may not benefit from neoadjuvant/adjuvant chemotherapy [21, 22]. This provided strong clinical rational for testing immunotherapy in patients with resectable MSI-H gastroesophageal cancer.

Nivolumab+ipilimumab

The NEONIPIGA was an investigator-initiated single arm phase II study evaluating the efficacy of neoadjuvant nivolumab+ipilimumab followed by adjuvant nivolumab in patients with resectable MSI-H/mismatch repair deficient (dMMR) gastroesophageal tumors [23]. A total of 32 patients were enrolled. Eight patients (32%) experienced grade 3/4 TRAEs during neoadjuvant treatment. In all, 29 patients underwent surgery, 2 refused surgery and had complete endoscopic response with tumor-free biopsies. All the 29 patients who underwent surgery had R0 resection: 17 (59%) had pathological complete response (pCR, primary endpoint) per local pathological assessment. Survival data were immature at the time point of the congress report.

Tremelimumab+durvalumab

As observed in NEONIPIGA trial, it is a matter of debate whether patients with complete response after neoadjuvant treatment would still need a surgical resection of the tumor. INFINITY is an ongoing phase II, multicenter, single-arm, multicohort trial investigating the activity and safety of tremelimumab+durvalumab as neoadjuvant (cohort 1) or definitive (cohort 2) treatment for centrally determined MSI-high/dMMR/EBV-negative, resectable gastroesophageal tumors [24]. Adjuvant treatment should be applied based on standard follow-up. A total of 31 patients, 18 in cohort 1 and 13 in cohort 2, will be enrolled. The primary endpoint of cohort 1 is rate of pCR and negative ctDNA after neoadjuvant immunotherapy and for cohort 2 the primary endpoint is 2-year complete response rate.

Discussion

Immunotherapy changed the treatment algorithm of gastroesophageal cancer in the advanced setting. However, the question remains whether chemotherapy could be completely omitted with combining different types of immune checkpoint inhibitors. The CheckMate-32 study assessed dual inhibition of anti-CTLA4 and PD-1 axis using nivolumab+ipilimumab [8]. Interestingly, the treatment arm with higher ipilimumab concentrations induced a remarkable ORR in heavily pretreated patients with gastroesophageal tumors; however, TRAEs were high, limiting the routine use of the combination with high doses of ipilimumab. The CheckMate-648 study evaluated nivolumab+ipilimumab as a chemotherapy-free regimen in patients with advanced ESCC and showed remarkable clinical outcomes compared to chemotherapy alone [5]. This led to the approval of nivolumab+ipilimumab in a biomarker-positive subset of patients with advanced ESCC. However, the presence of a crossover of the curves within the first 6 months of treatment was a critical concern. As is known for other tumor entities treated with immunotherapy, some patients may progress rapidly and even die within the first few months of treatment due to omission of chemotherapy [25, 26]. Therefore, the identification of the subgroup of patients and the critical assessment of the patient characteristics is of great importance for the selection of the appropriate treatment [10].

The success of nivolumab+ipilimumab was not observed in the CheckMate-649 study, in which patients with advanced gastroesophageal adenocarcinoma were examined [6]. The lack of a significant OS increase with nivolumab+ipilimumab is likely due to several reasons. Most importantly, tumors of gastric, GEJ (gastroesophageal junction), or esophageal adenocarcinoma consist of different molecular subtypes compared to squamous cell carcinoma. Further research is needed to understand how tumor biology, molecular heterogeneity, dynamics in the tumor microenvironment, and other patient characteristics affect the efficacy of combined PD-L1 and CTLA-4 blockade.

Notably, the small subset of patients with MSI-H, known for high tumor mutation load and CD8+ T cell infiltrates and prone to immune checkpoint inhibition [20], showed a significant benefit in OS and higher ORR during treatment with nivolumab+ipilimumab [6]. These data suggest that omission of chemotherapy and treatment with dual immune checkpoint blockade in this subgroup is feasible and should be explored in future studies.

In order to increase the effectiveness of single agents, the establishment of novel biomarker-driven immunotherapeutics is of great importance. Relatlimab, a novel anti-LAG3 antibody, is an emerging compound and its combination with nivolumab is attractive. However, a clinical trial testing the efficacy of this combination in advanced gastroesophageal cancer did not appear to meet its primary endpoint [14]. Hopefully, further clinical and biomarker analysis will help to identify patients who could potentially benefit from this combination. Another attractive biomarker is TIGIT, as preclinical and clinical studies suggested that dual targeting with anti-TIGIT and anti-PD-1 antibodies results in synergistic activation of immune cells and enhanced antitumor activity [17]. In this context, the SKYSCRAPER-07 study will show whether the combination of the anti-TIGIT drug tirogolumab and anti-PD-L1 inhibition with atezolizumab is useful in patients with ESCC after dCRT [18]. Another anti-TIGIT compound, ociperlimab, is being tested along with tislelizumab in advanced chemotherapy-refractory ESCC patients [19]. This Asia-based study includes non-Asian patients, so the results could impact non-Asian patient populations. However, it is also important to mention that TPS- or CPS-positive patients already receive immune checkpoint inhibitors as part of the first-line therapy. Since patients should be immunotherapy-naïve as an inclusion criterion for this study, very few patients will be candidates for the proposed treatment.

The subgroup of patients with MSI-H is not only of interest in the advanced setting. There is high clinical rationale for treating this subgroup with immunotherapy in resectable stages [21, 22]. In this regard, neoadjuvant treatment of patients with resectable MSI-H/dMMR gastroesophageal tumors with nivolumab+ipilimumab proved feasible and was associated with a high pCR rate [23]. Therefore, it might be worth further developing immunotherapy approaches for MSI-H tumors in resectable settings as part of a tissue-agnostic treatment strategy, as has been successfully implemented for advanced tumors [27]. Interestingly, this study included 2 patients whose endoscopic examination of the tumor revealed no viable tumor cells after neoadjuvant treatment, that the patients refused to undergo surgical removal of the tumor. From a clinical point of view, it is a matter of debate whether patients with a complete response after neoadjuvant treatment would still require surgical resection of the tumor. In this direction, the INFINITY study serves as a proof-of-concept to investigate neoadjuvant tremelimumab+durvalumab in patients with gastroesophageal MSI-H tumors and plans to omit surgical resection of the tumor if a complete endoscopic response is achieved after the neoadjuvant phase [24]. Decision-making is straightened with multiple biomarker analyzes and ctDNA investigations.

In addition to efficacy expectations, the focus should be set on the tolerability and health-related quality of life (HRQoL) issues of the dual immune checkpoint inhibition. In the case of a nivolumab+ipilimumab combination, higher ipilimumab doses led to higher ORR rates [8]. However increased rates

of adverse events including high immunotherapy-related adverse events (irAEs) raised critical concern. Therefore, careful dose selection and an improved awareness of the clinicians on the specific nature of irAEs are crucial. Initial assessments of HRQoL parameters show a maintained status throughout treatment with dual immune checkpoint inhibition and a trend toward reduced risk of deterioration [28]. Further evidence from future clinical trials is awaited.

In conclusion, dual immune checkpoint inhibition has so far become the standard of care for a subset of patients with advanced gastroesophageal tumors and shows promise for treating patients in earlier stages. Hopefully, further research into tumor biology will uncover more immune molecules that can be safely targeted along with existing immune checkpoint inhibitors. Some key parameters, including appropriate dosing, tolerability of treatment, greater magnitude of benefit without compromising quality of life, and acceptable financial toxicity, will be of further importance in interpreting the clinical results of the clinical trials.

Take home message

Dual immune checkpoint inhibitors show promising survival benefits in gastroesophageal tumors. Careful patient selection and biomarker-guided decision-making will improve survival outcomes.

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