Immune Checkpoint Inhibitors

Subjects: Immunology
Contributor: Anita Mazloom

There are several forms of Immune checkpoint inhibitors (ICIs) targeting at several checkpoint proteins or receptors including programmed cell death 1 (PD-1), PD-1 ligand (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), B and T cell lymphocyte attenuator (BTLA), V-domain Ig suppressor of T cell activation (VISTA), lymphocyte activation gene 3 (LAG3) and T cell immunoglobulin and mucin domain 3 (TIM-3) [5,6,7,8,9]. ICIs, specifically PD-1, PDL-1 and CTLA-4 inhibitors have been approved for the treatment of a variety of solid tumors, initially beginning with melanoma in 2011. Both PD-1 and CTLA-4 are negative costimulatory molecules that when inhibited enhance T cell activation and the eventual killing of tumor cells [10].
ICIs can be used in patients with chemotherapy-resistant tumors through tissue agnostic approval for MSI-H and high mutational burden tumors [14]. ICIs have shown that they are not only efficacious but have superior safety profile as well [15]. Most of the ICIs are well tolerated, however, they have distinct side effects compared to traditional cytotoxic chemotherapies [16,17].

Keywords: Immune Checkpoint Inhibitors ; microsatellite ; gastroesophageal ; coloerectal ; hepatocellular

1. Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of several solid and hematological malignancies. ICIs are not only able to produce long and durable responses, but also very well tolerated by patients. There are several approved indications of use of ICIs in treatment of metastatic gastrointestinal malignancies including gastric, esophageal, colorectal and hepatocellular carcinoma. In addition, ICIs can be used in microsatellite instability-high (MSI-H) and high tumor mutational burden (TMB) tumors in chemotherapy-resistant setting. Despite having good efficacy and superior safety profile, ICIs are clinically active in small subset of patients, therefore, there is a huge unmet need to enhance their efficacy and discover new predictive biomarkers.

2. Role of ICIs in First Line Setting

The standard of care first line therapy for esophageal and gastric cancers involves cytotoxic chemotherapy with the addition of anti-HER2 targeted therapy in cancers whose cells overexpress the receptor tyrosine kinase HER2. The preferred first-line regimen for unresectable locally advanced, recurrent or metastatic esophageal and gastric cancers is platinum-based therapy with a fluoropyrimidine backbone [22]. Two-drug cytotoxic regimens are generally preferred in this context owing to a decreased risk of toxicity. The role of checkpoint inhibitors has been evaluated in several trials; however, no approval has yet been granted for treatment in the first line setting. Below is a summary of the important clinical trials investigating the role of checkpoint inhibitors in the first line setting.

One of the major trials in first line setting was KEYNOTE-062, which was a phase III randomized clinical trial of 763 patients with advanced gastric or gastroesophageal junction cancer who were randomly assigned to either pembrolizumab at 200 mg every 3 weeks for up to 2 years, placebo plus chemotherapy or pembrolizumab plus chemotherapy (cisplatin and fluorouracil or capecitabine). All eligible patients had PD-L1 combined positive score (CPS) of at least 1. 37%. Of the study participants who had PD-L1 CPS of ≥ 10, 69% of patients had gastric cancer while 30% had GEJ cancer. The primary end point of the study was overall survival. The study demonstrated that overall survival for patients in the pembrolizumab arm was non-inferior to those receiving standard chemotherapy for patients whose tumors had a CPS ≥ 1. Overall, survival (OS) was superior to chemotherapy in the subset of patients receiving pembrolizumab whose tumors had a CPS score ≥ 10. Patient who had received pembrolizumab had median overall survival of 10.6 months compared with 11.1 months for those who received chemotherapy only. However, the pembrolizumab plus chemotherapy arm did not show superior overall survival or progression free survival (PFS) in patients with CPS ≥ 1 [23]. This study showed that single agent pembrolizumab has activity in first line setting, however, it lacks clinically meaningful activity when compared to chemotherapy in patients with CPS ≥ 1.

Another key trial that was performed in the first line setting was the phase III, JAVELIN Gastric 100 trial that compared maintenance therapy with the PD-L1 inhibitor avelumab to the continuation of first line chemotherapy. Patients whose tumors did not progress after 12 weeks of first line chemotherapy (oxaliplatin/fluoropyrimidine induction treatment) were randomly assigned to avelumab 10 mg/kg every 2 weeks and then switched to maintenance or continued on chemotherapy. The primary endpoint was OS post induction therapy in all randomized patients. A total of 499 patients were randomized in this study. The median OS post induction was 10.4 months in avelumab arm compared to 10.9 months in chemotherapy arm (95% CI 9.6–12.4), hazard ratio (HR) 0.91 (95% CI 0.74–1.11 p = 0.1779). The study failed to meet the primary objective as no overall survival benefit was observed in either the randomized or PD-L1 positive populations [24]. This study demonstrates no role of switch maintenance of avelumab in first line setting.

In the light of above data, chemotherapy remains the preferred standard of care treatment in first line setting.

3. Role of ICIs in Second Line Setting

There are several options available for systemic treatment in second line setting including cytotoxic chemotherapy and targeted therapy like the vascular endothelial growth factor (VEGF) inhibitor, ramucirumab. Similarly, checkpoint inhibitors have been evaluated for use in the second line setting.

The phase III KEYNOTE-061 trial investigated the use of pembrolizumab in 592 patients with advanced gastric or GEJ adenocarcinoma. Eligible patient had CPS ≥ 1 [25]. In this study, patients who had progression of disease after first-line treatment with platinum and fluoropyrimidine doublet therapy either received paclitaxel or pembrolizumab. Notably, patients with squamous cell or undifferentiated gastric cancer, as well as patients with prior immunotherapy were excluded from this study. In this study, pembrolizumab did not significantly prolong overall survival (median 9.1 versus 8.3 months). However, a subgroup analysis demonstrated a significant benefit for use of pembrolizumab over a taxane in patients with a deficient mismatch repair (dMMR) GEJ or gastric cancer. The FDA has approved pembrolizumab and nivolumab in any MSI-H patients with chemotherapy refractory disease. Therefore, pembrolizumab or nivolumab can be used in second line setting for MSI-H gastric or esophageal tumors. Due to this indication, it is imperative to check MSI in all patients.

Another major clinical trial was KEYNOTE-181 phase III trial. In this trial 628 patients with advanced or metastatic esophageal squamous cell carcinoma (SCC) or Siewert type I adenocarcinoma that had progressed after first-line chemotherapy were randomized to either pembrolizumab or the investigator's choice of standard chemotherapy with paclitaxel, docetaxel or irinotecan [26]. The three co-primary endpoints were OS in the intent-to-treat population, the squamous cell carcinoma subgroup and the subgroup with a CPS ≥ 10. There were 35% of the study population who had CPS ≥ 10. The study did not show OS benefit in intent to treat population. However, this study demonstrated that pembrolizumab significantly improved the median OS (9.3 vs. 6.7 months) in patients whose tumor had a PD-L1 CPS > 10. In July 2019, mainly based on the data from this trial, the FDA approved pembrolizumab in patients with recurrent locally advanced or metastatic SCC of the esophagus who progressed after one or more lines of chemotherapy.

Nivolumab has also been studied in second line setting in advanced SCC of esophagus. ATTRACTION-3 was phase III randomized multicenter clinical trial that randomly assigned 419 patients to either nivolumab or investigator's choice of chemotherapy (paclitaxel or docetaxel). The primary endpoint was overall survival. The study demonstrated an improved overall survival in patients with previously treated esophageal SCC who received nivolumab versus chemotherapy, irrespective of PD-L1 expression. The median OS was 10·9 months compared to 8.4 months in chemotherapy arm. (HR 0·77, 95% CI 0·62–0·96; p = 0·019) [27,28]. Based on these results, FDA approved nivolumab for patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after progression on fluoropyrimidine and platinum-based chemotherapy.

4. Role of ICIs in Third Line Setting

Pembrolizumab has been approved in third line setting for gastric or gastroesophageal adenocarcinoma. The approval was based on KEYNOTE-059 trial. This was a phase II, single-arm, multicohort study. The primary endpoint was response rate. 259 patients were enrolled into this study, the objective response rate was 11.6% in all patients while it was 15.5% in PD-L1 positive patients. FDA approved pembrolizumab for PD-L1 expressing gastric and gastroesophageal adenocarcinomas after progression on or after two or more prior systemic therapies, including fluoropyrimidine- and platinum-containing chemotherapy [29].

5. Ongoing Trials

There are several ongoing clinical trials of ICIs in gastric and esophageal cancers that incorporate immunotherapy. Check-Mate 649 (NCT 02872116) is an ongoing randomized phase III study investigating the use of immunotherapy in previously untreated advanced or metastatic gastric or GEJ cancer. In this study, nivolumab alone—or nivolumab plus ipilimumab in combination with systemic chemotherapy—is being compared to systemic chemotherapy alone in patients who have not received neoadjuvant or adjuvant treatment within the last six months [30]. The primary endpoint is OS in patients with PD-L1 (≥1%) tumors with secondary endpoints including OS in all patients, PFS and time to symptom deterioration in all patients and in those with PD-L1 positive tumors and safety. In addition, there several combination trials of ICIs with other targeted therapies including tyrosine kinase inhibitors and VEGF inhibitors are currently enrolling patients. There are several trials that are combining ICIs with other agents especially immuno-modulating drugs along with radiation therapy to enhance the efficacy of ICIs in gastroesophageal tumors. There are few trials looking at the role of oncolytic virus in combination with ICIs to enhance their efficacy [31]. The role of checkpoint inhibitors in first line setting is being investigated in KEYNOTE-811 (NCT03615326), which is an ongoing randomized, double-blinded phase III trial comparing standard of care chemotherapy (SOC) in combination with trastuzumab versus SOC chemotherapy in combination with pembrolizumab plus trastuzumab in HER-2 positive advanced gastric and gastroesophageal cancer. SOC is defined as Cisplatin on Day 1 and 5-FU on Day 1–5 of each 3-week cycle and [32]. The results of several ongoing trials will likely help expand the role of immunotherapy in management of gastroesophageal tumors.
