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Review

Recent Advances in Immunotherapy in the Treatment of Gastrointestinal Tract Cancers

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Abstract

Immunotherapies (ICI) are used alone, in combination with chemotherapy (CT) or targeted therapy in many cancers. All current developments will be reviewed in gastrointetsinal tract tumor treatment.

Keywords: ICI, gastrointestinal tract tumor traetment, update

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As in many cancers, immunotherapy is strengthening its position day by day in the treatment of gastrointestinal system cancers, with promising results of new studies. In this review, the current treatment recommendations will be shared with the results of immunotherapy studies performed in the esophageal, gastroesophageal junction (GEJ), gastric, and colorectal cancers.

Esophagus/Gastroesophageal Junction and Gastric Cancers

CheckMate-577, a study conducted in stage II–III esophageal (squamous or adenocancer) and GEJ cancers, was presented at ESMO-2020, and for the first time, immunotherapy was included in the guidelines for early stage gastrointestinal system cancers. In this study, it was shown that a twofold disease-free survival advantage was achieved with the use of 1-year nivolumab (NIVO) treatment in the adjuvant setting for patients who had residual disease after preoperative chemoradiotherapy followed by surgery. The proportion of patients with Programmed death-ligand 1 (PD-L1) expression < 1% was 70%. Based on the findings of this study, adjuvant NIVO is recommended regardless of PD-L1 expression.[1]

The ATTRACTION-3 study was a multicenter, randomized, open-label, and phase 3 study. In this study, the effectiveness of NIVO versus taxane chemotherapy (CT) was investigated in patients with advanced esophageal cancer (squamous) who were refractory or intolerant to previous CT. The primary endpoint of the study was overall survival (OS). NIVO was effective in terms of OS in all patient groups; however, in the subgroup analysis, the largest benefit was observed in the patients with PD-L1 expression >1% [(NIVO vs. CT; mOS; 10.9 vs. 8.1 months, hazard ratio (HR) (95% confidence interval (CI) = 0.69 (0.51–0.94)].[2] Relying on the efficacy and safety data of this study, Food and Drug Administration (FDA) and European Medicines Agency approved NIVO in patients with unresectable, recurrent, or metastatic squamous subtype esophageal cancer who previously received fluoropyrimidine and platinum-based CT.

At ASCO-GI 2020, the 3-year survival results of the ATTRACTION-2 study were announced. In this phase 3 study by Chen et al. which included 49 centers from Asian countries, the effectiveness of NIVO versus placebo was investigated. Patients with unresectable, advanced, or recurrent gastric and GEJ adenocarcinoma who received 2 or more lines of CT regimens were included; the primary endpoint was OS. At 3-year follow-up, the median OS was 5.26 months in the NIVO group versus 4.12 months in the placebo, with HR (95% CI) = 0.62 (0.50–0.75), p<0.0001. In patients

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with complete or partial response, the OS advantage favored NIVO arm. There was also a numerical superiority in OS for patients with stable disease in the NIVO arm. Side effects were seen frequently in the first 3 months, and OS was found to be higher in patients who had side effects related to NIVO. In this study, the use of NIVO also provided an OS advantage with a good safety profile at 3-year results in patients with unresectable, advanced stage, or recurrent gastric and GEJ adenocarcinoma who received at least two lines of CT regimens.[3]

The KEYNOTE-061 study was a phase 3 study comparing pembrolizumab (PEMBRO) monotherapy to taxane-based CT in patients with advanced or unresectable gastric and GEJ adenocarcinomas with PD-L1 expression, who received a prior fluoropyrimidine and platinum-based CT. Although the results in ASCO-2020 showed fewer side effects and increased response rate by elevated PD-L1 expression, the use of PEMBRO was not superior in terms of OS and progression-free survival (PFS) when the combined positive score (CPS), which was the primary endpoint of the study evaluating PD-L1 expressions in both tumor and tumor-associated immune cells, was evaluated separately as CPS ≥1, ≥5, and ≥10. The findings of the study were also confirmed by 2-year follow-up results.[4]

The KEYNOTE-062 study was a phase 3 study, the results of which were announced at ASCO-2019. In addition to the study arms in KEYNOTE-061, the third arm including PEMBRO + CT was added. As compared with CT, PEMBRO was safe and noninferior in terms of OS when CPS ≥1 and provided additional improvement in OS when CPS ≥10. When compared PEMBRO + CT with CT, although the addition of PEMBRO to CT did not increase toxicity, no significant contribution in OS was observed, with a moderate increase in PFS and objective response rate (ORR) when assessing CPS separately as ≥1 or ≥10. As a result of this study, PEMBRO compared with CT was safe and it provided equal OS when CPS ≥ 1 but improved OS when CPS ≥1.[5]

CheckMate-649 was one of the most intriguing phase 3 studies in the ESMO-2020 congress. Based on the fact that NIVO provides OS advantage in previously treated advanced esophageal, gastric, and GEJ cancers, the benefit of adding NIVO to CT was investigated in the first-line treatment in these disease groups. In the study, 60% of patients had CPS >5 and 80% had CPS ≥1 disease, namely 80% patients had CPS ≥1 disease. The minimum follow-up time of the study was 12.1 months, with a median duration of 6.8 months of NIVO treatment. It was shown that adding NIVO to CT improved both OS and PFS. In subgroup analysis for OS and PFS, the increase was significant in CPS ≥5, CPS ≥1, and in all subgroups. The largest improvement was reported in the CPS ≥5 group, which was the value determined in the study design as the primary endpoint for OS and PFS.[6]

Another study in ESMO-2020 was the ATTRACTION-4 study, a phase 3 study with the participation of 130 Asian and Japanese centers, with the same design as the European CheckMate-649 study. The proportion of patients with PD-L1 expression < 1% was 84%. Although the CPS score was not checked, a greater rate of patients who did not have PD-L1 expression in the tumor was included in this study, as compared with CheckMate-649. The PFS, ORR, and durable of response were observed to be improved, with no significant OS advantage.[7]

Another study, which was conducted in a patient group similar to CheckMate-649 presented in ESMO-2020, was the KEYNOTE-590 study. In the study, the addition of PEMBRO to CT was investigated in the first-line treatment of patients with metastatic or unresectable esophageal (squamous cell or adenocarcinoma) and GEJ (Siewert 1) cancers. In the results of the study, the addition of PEMBRO to CT was shown to be effective in terms of OS, PFS, and ORR, with a good safety profile. The benefit was observed in all patient groups, with the greatest benefit being observed in patients with CPS ≥10.[8]

In light of the findings from the CheckMate-577 study, the NCCN guideline recommends the use of adjuvant NIVO treatment in patients with stage II–III esophageal (adenocancer and squamous) and GEJ cancers who have residual disease after preoperative chemoradiotherapy followed by surgery.[9]

NCCN guideline recommends the addition of NIVO to fluoropyrimidine (capecitabine or 5-FU) and oxaliplatin-based CT for treatment-naive patients with HER2 negative unresectable or advanced gastric, esophageal, and, GEJ adenocarcinomas with CPS ≥5 determined as the primary endpoint of the CheckMate-649 study. In cases where immune checkpoint inhibitors (ICI) are not used in the first-line setting, the use of NIVO in the subsequent step is recommended according to the results of the ATTRACTION-3 study, in which the efficacy was shown in esophageal cancer with squamous subtype.[9]

In the NCCN guideline, the addition of PEMBRO to fluoropyrimidine and platinum (with a higher level of evidence for cisplatin versus oxaliplatin because of the preferred platinum agent in the study)-based CT is recommended in patients with HER2 negative esophageal (squamous and adenocancer) and GEJ adenocarcinomas with CPS ≥10, where the largest benefit was observed in KEYNOTE-590 study. In cases where ICI are not used in the first-line setting, the use of PEMBRO is recommended in third or further line setting in patients with esophageal, gastric, and GEJ adenocarcinomas with CPS ≥1 (KEYNOTE-012 Phase 1B and KEYNOTE-059 Phase 2, FDA 2017 approved),[10,11] and in second or further line setting in patients with esophageal squamous subtype with CPS ≥ 10 (KEYNOTE-180 Phase 2 and KEYNOTE-181 Phase 3, FDA 2019 approved).[12,13] PEMBRO, as a tumor agnostic therapy in all upper gastrointestinal tract tumors, is recommended in the presence of high microsatellite instability (MSI-H) or DNA mismatch repair deficiency (dMMR) and tumor mutation burden ≥10 mutations/megabase.[9]

Colorectal Cancer

The incidence of MSI-H or dMMR in metastatic colorectal cancer (mCRC) is detected at a rate of 3.5%–6.5%, and ICI is indicated in the treatment of this patient group. There are studies on the use of immunotherapy in the microsatellite stability patient group, particularly in patients treated by rechallenge therapy. Although promising, it has not changed the daily practice and hence has not found its place in the guidelines.[14]

NIVO was used as a monotherapy in CheckMate-142, which was a phase 2, multicohort, and nonrandomized study. In the results of 74 patients, after a long follow-up period of 21 months, it has been shown that NIVO provides a sustained response and disease control in the treatment of patients with MSI-H or dMMR mCRC who progressed after treatment with fluoropyrimidine, oxaliplatin, and irinotecan, and hence has entered clinical use as a treatment option in this patient group. In another cohort of this study, the effectiveness of low-dose (1 mg/kg, once every 6 weeks) ipilimumab (IPI), a monoclonal antibody developed against cytotoxic T-lymphocyte-associated protein-4, in addition to NIVO (3 mg/kg, once every 2 weeks) was investigated until progression in the first-line setting in patients with MSI-H or dMMR mCRC. Considering the patients included in the study, the rate of right colon cancer was 58%, and the percentage of patients with RAS/BRAF mutation was 60%. ECOG performance score was 0–1, and the primary endpoint was ORR. Patients with poor prognosis and good performance scores were included in the study. A durable and sustained clinical response was seen at a 29-month follow-up. Efficacy was demonstrated in all patient subgroups. Grade 3–4 toxicity was observed in 22% of the patients. Therefore, this combination is considered as an alternative therapy to PEMBRO in the first-line setting in patients with MSI-H or dMMR mCRC.[15–17]

The KEYNOTE-177 study has been introduced as the most influential study among immunotherapy studies of mCRC. In the study, the use of PEMBRO in the first-line setting of patients with MSI-H or dMMR mCRC was compared with CT. PEMBRO provided a twofold increase in PFS as well as improved quality of life and reduced toxicity. Median progression-free survival 1(mPFS1) was 16.5 months in the PEMBRO arm and 8.2 months in the CT arm [HR (95% CI) = 0.60 (0.45–0.80), p = 0.0002]. PFS at 24 months was 48.3% in the PEMBRO arm and 18.6% in the CT arm. In terms of ORR, the superiority was in the PEMBRO arm (43.8% vs. 33.1%). About 36% of the patients who received first-line CT were switched to the PEMBRO arm after progression. In the evaluation of mPFS2, a clinically significant improvement was demonstrated in the PEMBRO arm, with mPFS2 of 23.5 months in the CT arm versus not reached in the PEMBRO arm. The results of the KEYNOTE-177 study recommend the use of PEMBRO in the first-line treatment in patients with MSI-H or dMMR mCRC.[18]

The NCCN guideline recommends PEMBRO as the preferred treatment regimen for MSI-H or dMMR mCRC. The other treatment option is NIVO ± IPI. If intensive treatment is not feasible in the same group, PEMBRO or NIVO is recommended.[19]

In conclusion, the use of adjuvant NIVO treatment has entered daily practice in the presence of residual disease in patients with early stage esophageal and GEJ cancer treated with preoperative chemoradiotherapy followed by surgery. In HER2 negative upper gastrointestinal system tumors, it is recommended to add ICI to CT; if ICI is not used in the first-line setting, it is recommended to be used in subsequent settings. PEMBRO is recommended as a tumor agnostic therapy for upper gastrointestinal system tumors. PEMBRO (preferably) or NIVO ± IPI is recommended as the first-line therapy in patients with MSI-H or dMMR mCRC.

Disclosures

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