Immune Checkpoint Inhibitor in Gastrointestinal Tumors

Subjects: Oncology

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Immune checkpoint inhibitors (ICIs) are now incorporated into the management of GI tumors. The heterogenous nature of these tumors, however, reveals a lack of ICI consistency in effectiveness. Certain biomarkers have emerged as being potentially predictive for ICI effectiveness.

gastrointestinal neoplasms immune checkpoint inhibitor microsatellite-instability-high/deficient mismatch repair

1. Introduction

Gastrointestinal (GI) tumors, cancers occurring in the digestive tract, encompass an array of heterogeneous solid tumors. GI tumors consist of some of the most commonly diagnosed malignancies (i.e., colon cancer, rectal cancer, pancreatic cancer, hepatocellular carcinoma, gastric cancer, and esophageal cancer) and encompass some rare tumor entities (i.e., anal, biliary tract cancers, gallbladder, appendiceal, duodenal, etc.). These tumors differ considerably in their risk factors, location, histological characteristics, molecular profile, and management. Additionally, each tumor type has many heterogeneous subtypes.

Molecular profiling has expanded the understanding in identifying targets and predictive biomarkers. This is true for GI tumors. Like other solid tumors, immune checkpoint inhibitors (ICIs) are now being incorporated into treatment; however, not all patients respond similarly. Continued exploration of biomarkers remains of utmost importance to determine the best ICI precision medicine in GI tumors.

2. Microsatellite Instability-High/Deficient Mismatch Repair (MSI-H/dMMR)

DNA MMR machinery is essential for the maintenance of genomic stability. The MMR machinery is composed of MSH2/MSH6 and MSH2/MSH3 that recognize single-nucleotide mismatches and small insertion/deletions that occurs during DNA replication. Subsequently hMLH1/hPMS1 Homolog 2, (hPMS2), hMLH1/hPMS1 Homolog 1(hPMS1) and hMLH1/hMLH3 are recruited to catalyze the excision and resynthesize the mismatch [1]. The dysfunction of this system, namely dMMR, results in an errors in microsatellites which consist of repeated DNA sequences of 1–6 nucleotides [2]. Thus, the alteration of the number of microsatellites sensitizes a dMMR state. This is referred to as microsatellite instability (MSI). MSI is thought to be involved in tumorigenesis and tumor

proliferation due to the accumulation of repair-associated mutations in genes for tumor suppression, cell proliferation, DNA repair, apoptosis. Clinically, it can be categorized as MSI-H and MSI-low or stable (MSS) according to the frequency of MSI [3]. In sporadic dMMR tumor, it is mainly caused by MMR gene mutation due to acquired hypermethylation of the promoter region of *MLH1* gene, leading to decreased expression of MMR protein [4]. On the other hand, the Lynch syndrome, which takes the form of autosomal dominant inheritance, is caused by germline mutations of the MMR-regulated genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or a deletion of the *EPCAM* gene adjacent to the upstream of the *MSH2* in one allele [5][6][7].

MSI-H/dMMR solid tumors are found in various organs [8][9]. The frequency of MSI-H/dMMR in colorectal cancer (CRC) is reported to be approximately 15% [10] with Lynch syndrome-associated CRC accounting for ~20–30% of cases and sporadic MSI-H/dMMR CRC being ~70–80% of cases [11]. The frequency of MSI-H/dMMR CRC varies according to stage (~20% stage I/II, 12% stage III, and 5% in stage IV) [12]. MSI-H/dMMR CRC is more common in the right colon and the proportion of poorly differentiated adenocarcinoma is high [13]. Moreover, BRAF V600E gene mutation is found in 35–43% of MSI-H/dMMR CRC [14][15]. Since BRAF V600E gene mutations are rarely found in the Lynch syndrome-related CRC, BRAF screening in MSI-H/dMMR CRC helps to distinguish sporadic MSI-H/dMMR tumor or Lynch syndrome [16].

In gastric cancer (GAC), MSI-H/dMMR has a frequency of ~20% [17][18]. As well as MSI-H/dMMR CRC, the prevalence depends on tumor stage; the highest in node-negative stage (20%) and the lowest in metastatic disease (<5%). In esophageal adenocarcinoma (EAC), MSI-H/dMMR can be observed 3–5% due to somatic mutation since Lynch syndrome associated esophageal adenocarcinoma (EAC) is rare [19]. Regarding gastroesophageal junction (GEJ) cancer, those in Siewert type II and III are related to MSI-H/dMMR [20]. In small bowel cancer, the frequency of MSI-H/dMMR is reported to be 5–45%, which is a relatively big range and frequency [21]. MSI-H/dMMR is also associated with other GI tumors at a lower incidence (i.e., ~2–2.5% pancreatic; ~2% biliary; ~2% gallbladder, etc.) and even more rarely seen in some (Hepatocellular carcinoma (HCC) and anal cancer given different cancer etiologies) [22][23][24].

MSI-H/dMMR tumors are generally associated with a high neoantigen burden, highly immunogenic, and thus thought to respond to ICI therapy. A current exciting pathway for these tumors is initial investigation with localized MSI-H/dMMR solid tumors and the potential for organ-sparing (non-operative) approach. Cercek et al. recently published results of locally advanced MSI-H/dMMR rectal cancer patients (n = 12) who received anti-programmed death-1 (anti-PD-1) agent ICI, dostarlimab [25]. All patients had a clinical complete response (cCR). Currently, no patients had received chemoradiation (CRT), undergone surgery, progressed, or had recurrence. Additionally, Ludford et al. reported initial results giving pembrolizumab to MSI-H/dMMR tissue agnostic localized primary tumors (n = 32) [26]. Tumor types included 24 CRC and 8 non-CRC (1 endometrial, 1 gastric, 1 meningeal, 2 duodenal, 1 ampullary, 2 pancreatic). Among 30 evaluable pts, overall response rate (ORR) was 77% with 30% CR, 47% PR, 20% stable disease, 3% progression. Pathological CR (pCR) was noted in 50% of the six patients that underwent surgery. An organ-sparing approach was chosen in 15 patients and two patients had reached one year of avoiding surgery. Additionally, an ICI shift in upfront treatment for advanced MSI-H/dMMR CRC has been a recent development [27]. These patients are now recommended pembrolizumab monotherapy given superiority over

chemotherapy seen in KEYNOTE-177. In the KEYNOTE-158, a phase 2 pembrolizumab study, an ORR of 40.9%, a median progression-free survival (PFS) of 4.2 months, and median OS of 24.3 months was seen in advanced, pre-treated MSI-H/dMMR biliary tract cancers (*n* = 22) [28]. Although dMMR/MSI-H status for GI cancer has become a biomarker that determines an indication for ICIs, factors associated with resistance are still being investigated. Further research would suggest more implications for the role of dMMR/MSI-H status as a predictive marker for immunotherapy but determine why certain MSI-H/dMMR patients do not respond will be the key to moving forward. It is believed tissue-agnostic trials of MSI-H/dMMR tumors will provide answers in a quicker fashion. Exciting trials are underway in both the localized MSI-H/dMMR rectal, colon, and gastric setting and metastatic solid tumor setting as these patients will need differing treatment strategies than those proficient in MMR/MSS. Phase 3 trials in this space are described in **Table 1** [29][30][31][32][33][34][35].

Table 1. Microsatellite Instability-High/Deficient Mismatch Repair (MSI-H/dMMR) Phase 3 Trials in Gastrointestinal Malignancies [29][30][31][32][33][34][35].

Trial Identifier	ICI Therapy	Phase	Patient Population	Setting
NCT02997228	Atezolizumab +/− bevacizumab with chemotherapy	3	CRC	Metastatic
NCT04008030	Nivolumab +/− ipilimumab or chemotherapy	3	CRC	Metastatic
NCT05239741	Pembrolizumab vs. chemotherapy	3	CRC	Metastatic
NCT05236972	Sintilimab vs. CapeOx	3	CRC	Postoperative
NCT04304209	Sintilimab +/− chemotherapy	2/3	CRC	Preoperative/Watch and wait
NCT03827044	Avelumab + chemotherapy	3	Colon cancer	Postoperative
NCT05002686	Sintilimab + chemoradiation	2/3	Gastric cancer	Preoperative

CRC: colorectal cancer.

3. Programmed-Death Ligand-1 (PD-L1) Expression

Given the role that PD-L1 plays in tumor immune escape, its expression has emerged as a potential biomarker to test the effectiveness of ICI. PD-L1 expression is a current exploration amongst GI tumors to determine if this holds an ICI predictive role.

For upper GI patients (gastric and esophageal patients), PD-L1 expression and ICI response is of much debate given conflicting results seen in CHECKMATE 649, KEYNOTE-811, ATTRACTION-4, JAVELIN, and ORIENT-16 [36][37][38][39][40]. These trials are described in detail in **Table 2**. Currently, for upper GI tumors, researchers feel PD-L1 expression (method and degree of positivity) needs more standardization across trial designs to determine the

predictive value. It is clear with the current data that additional new biomarkers and correlating with other clinicopathological features are needed to determine those likely to benefit in the high PD-L1 combined positive score (CPS) patients. As this appears at present time not to be the ideal biomarker alone to determine ICI response.

Table 2. Programmed-Death Ligand-l Expression with Immune Checkpoint Inhibitors in Gastric Cancer [36][37][38][39][40].

Trial Name/Identifier	ICI Therapy	Phase	Setting	Results
CHECKMATE-649 NCT02872116	Chemotherapy +/− nivolumab	3	Metastatic PD-L1 not inclusion criteria. Results reported by CPS score	Median OS: CPS ≥ 5: 14.4 months vs. 11.1 months CPS < 5: 12.4 months vs. 12.3 months Any CPS: 13.8 months vs. 11.6 months Median PFS: CPS > 5: 7.7 months vs. 6.0 months Any CPS: 7.7 months vs. 6.9 months
KEYNOTE-811 NCT03615326	Trastuzumab + chemotherapy +/− pembrolizumab	3	Metastatic PD-L1 not inclusion criteria	ORR: 74.4% vs. 51.9% Complete response: 11.3% vs. 3.1%
ATTRACTION-4NCT02746796	Chemotherapy +/− nivolumab	2/3	Metastatic PD-L1 not inclusion criteria Results not defined by CPS score (only ~15% in each group had PD-L1 expression ≥ 1)	Median OS: 17.45 months vs. 17.15 months Median PFS: 10.45 months vs. 8.34 months
JAVELIN Gastric 100 NCT02625610	Avelumab maintenance therapy vs. continued chemotherapy	3	Metastatic PD-L1 not inclusion criteria Results described by PD-L1 expression and CPS	Median OS: All patients: 10.4 months vs. 10.6 months PD-L1 ≥ 1% expression: 16.2 months vs. 17.7 months PD-L1 CPS ≥ 1: 14.9

Trial Name/Identifier	ICI Therapy	Phase	Setting	Results
				months vs. 11.6 months
ORIENT-16 NCT03745170 [41]	Chemotherapy +/− sintilimab	3	Metastatic PD-L1 not inclusion criteria Results reported by CPS	Median OS: All patients: 15.2 months vs. 12.3 months CPS ≥ 5: 18.4 months vs. 12.9 months

PD-L1: programmed death ligand-1; OS: Overall survival; CPS: combined positive score; PFS: progression free survival.

biomarker relevance will be needed soon; however, in advanced biliary tract tumors as results of the phase 3 gemcitabine plus cisplatin +/− nab-paclitaxel, results are expected soon [43]. Determining who would benefit most from ICIs might help determine the best upfront therapy if this trial's results are favorable. Controversial results are noted for HCC. CHECKMATE-459, nivolumab compared to sorafenib, those with PD-L1 positive reported higher ORR [44]. While CHECKMATE-040 showed no statistical difference [45]. Of significance are updated results of the IMbrave150. IMbrave150 established atezolizumab and bevacizumab are standard front-line treatment for advanced HCC. An updated retrospective look at the tissues in this research showed that PD-L1 expression is likely of limited predictive value to determine benefit with atezolizumab and bevacizumab (median overall survival (OS) 12.6 months PD-L1 ≥1%; median OS 15.4 months for PD-L1 <1%) [46]. Additionally, results of the HIMALAYA trial of tremelimumab and durvalumab are expected to be added to the treatment choices for upfront HCC [47]. PD-L1 expression in relation to outcomes in HIMALAYA lacked reporting thus limit determination of an ICI predictive link.

For squamous cell carcinoma of the anal canal (SCCA), single agent ICIs (nivolumab or pembrolizumab) are options for refractory metastatic anal cancer [48][49]. PD-L1 expression was not required in the studies evaluating the use of these agents in this refractory patient population; however, exploratory analysis suggests higher response in those with PD-L1 expression [48]. These data, however, remain too immature for any value.

There is much work needed at understanding the predictive role of PD-L1 expression regarding ICI GI therapy as currently it has not been as precise as hoped. Questions remaining include (1) determining the standard definition for PD-L1 expression, (2) what tumor should be tested (fresh; archived) (3) why does expression not correlate to response (4) why do some non-PD-L1 expressing tumors shrink (5) is expression altered by prior therapy (6) does PD-L1 expression drive immunogenicity in the same fashion across tumors? For now, it is believed PD-L1 expression correlation remains too vague for most GI tumors and continued exploration is needed to determine the role in each tumor type.

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