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EDITORIAL

Checkpoint inhibitors in gastrointestinal cancers: Expectations and reality

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Abstract

Immune checkpoint inhibitors represent revolutionary anti-cancer agents, being rapidly approved in different malignancies and settings. Gastrointestinal (GI) cancers represent a wide variety of tumors with specific characteristics and different responses to various therapeutic alternatives; while some are chemo-sensitive others are chemo-resistant and only respond to more aggressive cytotoxic regimens, targeted therapies or a combination of both. Preliminary results of immune checkpoint inhibitors in some GI cancers are promising, namely in hepatocellular carcinoma, anal cancers and microsatellite instability high colorectal cancers. An impressive instead of a impressive number of immune checkpoint inhibitors are being evaluated in different indications in GI cancers as single agents or in combination with other agents. We reported in this paper ongoing and published trials evaluating immune checkpoint inhibitors in hepatocellular carcinoma and biliary tract cancers, esophageal, gastric, pancreatic, colorectal and anal cancers and we discussed the future perspectives of these agents in GI cancers.

Key words: Immunotherapies; Cancers; Digestive; Checkpoint inhibitors; Gastrointestinal

Core tip: Immune checkpoint inhibitors represent new promising anti-cancer therapies, rapidly approved in different malignancies and settings. We aimed in this editorial to report all the ongoing and published trials evaluating these agents in gastro-intestinal malignancies, to focus on the past expectations and the reality of the results and finally, to discuss the future perspectives of these agents in this field.

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INTRODUCTION

Since the emergence of immune checkpoint inhibitors (ICI) in the last few years, hundreds of trials have been attempting to test their efficacy in the treatment of various malignancies and in different settings[1]. Melanomas, non-small cell lung cancer (NSCLC), renal cell carcinomas and bladder cancer are the three malignancies, where these agents have presently gained approval, mainly in metastatic as first line treatment in melanomas and in the second line setting for the three others[2-5]. Most importantly, one of these agents, ipilimumab, has been approved in the adjuvant setting for the treatment of melanoma[6].

Similar response rates (RR) have been reported in different malignancies ranging between 15% to 25%, except for sarcomas, colorectal cancers (CRC), pancreatic, breast and prostate cancers, where efficacy has not been demonstrated or is still under evaluation in clinical trials. Preliminary results from phase 1 and 2 trials are reporting response rates between 15% to 25% in esophageal, gastric, hepato-biliary and anal cancer, similar to those described in other malignancies. Two exceptions in gastrointestinal (GI) cancers are pancreatic and CRC. In pancreatic cancer, we still do not have any preliminary results from trials looking into anti-PD1 agents and those evaluating anti-CTLA4 agent were mostly disappointing[7]. After several trials failed to demonstrate the value of ICI in CRC, it was initially believed that these agents would not easily find their way into the preexisting the therapeutic arsenal. It was only after one patient with MMR-deficient CRC demonstrated a spectacular response to anti-PD1 agent that a potential predictive biomarker was brought to light. Effectively, the RR in this subgroup of patients exceeded 40%[8].

Despite the promising results in GI malignancies, ICI have not yet been approved in any of the aforementioned tumors. Herein, we briefly summaries the results of select trial with results that might have an impact on our clinical practice in the foreseeable future (Table 1).

CHECKPOINT INHIBITORS RESULTS IN GI CANCERS

Esophageal cancer

Results from two phase Ⅱ trials evaluating nivolumab and pembrolizumab in esophageal cancers demonstrated an acceptable safety profile, meaningful clinical activity and RR of around 20% in heavily pretreated patients[9]. Nivolumab is evaluated in squamous cell carcinoma regardless of PD-L1 status, while pembrolizumab is mainly being tested in patients with squamous cell carcinoma (77%), but PDL1 positivity was set as an inclusion criteria[10].

Gastric cancer

In gastric adenocarcinomas, tremelimumab (anti-CTLA4) showed a response rate of 5% in a phase Ⅰ trial[11]. A phase Ⅱ trial testing nivolumab in pretreated metastatic adenocarcinoma of the stomach and the gastroesophageal junction reported response rates around 12%, independently of the PDL1 status[12], while a phase Ⅰb trial evaluating pembrolizumab in pretreated metastatic adenocarcinoma of the stomach and the junction showed response rates exceeding the 30% in PD-L1 positive patients[13]. In ASCO 2016, a trial tested avelumab as second line treatment and as maintenance treatment of advanced gastric or gastro-esophageal junction, the RR in second line setting was 18% in PD-L1 positive tumors and 9% in PD-L1 negative tumors; the disease control rate (DCR) was 29%[14]. The combination of ipilimumab and nivolumab was tested at two different doses in phase Ⅰ/Ⅱ trial in gastric or gastro-esophageal adenocarcinoma, progressing after chemotherapy; the RR was 26% with the combination of nivolumab 1 mg/kg and ipilimumab 3 mg/kg and 14% with nivolumab[15].

Pancreatic

A phase Ⅱ trial evaluating ipilimumab in pancreatic cancer failed to discern any clinical activity as no response were reported in a any of the 26 patients (0%)[7]. Moreover, we do not have any preliminary results with anti-PD1 agents; three ongoing trials are evaluating nivolumab as single agent, nivolumab in combination with ipilimumab and nivolumab in combination with gemcitabine, which might act as a stimulant for neo-antigen expression.

Hepatocellular and biliary tract carcinoma

The safety profile and antitumor activity tremelimumab, in patients with hepatitis-C-induced liver cirrhosis and subsequent advanced hepatocellular carcinoma (HCC), was promising with RR of approximately 17% and stable disease of 76%[16]. Additionally, Nivolumab was tested in patients with sorafenib-refractory or sorafenib-intolerant HCC regardless of hepatitis status. Preliminary results were promising with RR of 23% (15% in uninfected and 32% in infected HCC)[17]. Not only do these trials highlight the efficacy of ICI in this subset of patients, but they also provide valuable information in regards to the potential use of immunotherapy in patients with less than vigorous liver function. An ongoing trial randomized, multicenter, phase Ⅲ study is comparing nivolumab to sorafenib in first-line treatment in patients with advanced hepatocellular carcinoma (NCT02576509).

Pembrolizumab was also tested in pretreated, PDL1 positive, adenocarcinoma of the gallbladder and biliary tract - excluding ampullary carcinomas - with promising results; RR of 17% and SD of 17%[18].

CRC

As previously mentioned, various phase Ⅰ trials of anti-CTLA4 or anti-PD1 agents in CRC came to naught,

Table 1 Summarizes publish and ongoing clinical trials evaluating checkpoint inhibitors in gastrointestinal cancers

Ref.	Phase/*n*	Agent	Histology distribution	Chemotherapies	ORR	SD	OS
Esophageal cancer							
Kojima *et al*[9], 2016	Ⅱ/65	Nivolumab	100% squamous	Median prior regimen 3	17.20%	25%	12.1
Doi *et al*[10], 2015	Ⅰb/23	Pembrolizumab	77% squamous	87% received ⩾ 2 prior therapies for metastatic disease	23%	18%	N/A
Gastric cancer							
Ralph *et al*[11], 2010	Ⅱ/18	Tremelimumab	Adenocarcinoma (gastric and esophageal)	15 received one line, 3 two lines	5%	22%	N/A
Muro *et al*[13], 2016	Ⅰb/39	Pembrolizumab	Adenocarcinoma of the stomach and the junction	Pretreated	31%	NA	11.4
Le *et al*[12], 2016	Ⅱ/59	Nivolumab	Adenocarcinoma of the stomach and the junction	83 % received ⩾ 2 prior therapies for metastatic disease	12%	21%	6.8
Chung *et al*[14], 2016	Ⅰb/62	Avelumab	Adenocarcinoma of the stomach and the junction	Second line treatment	18.2 (PDL1+)	NA	6.3 (PDL1+)
Janjigian *et al*[15], 2016	Ⅰ/Ⅱ/160	Nivolumab N(3) + I (1) N(1) + I (3)	Adenocarcinoma of the stomach and the junction	⩾ 2 prior therapies for metastatic disease	14% 10% 25%	NA	5.0 4.6 6.9
Pancreatic cancer/hepatocellular carcinoma/biliary tract cancers							
Royal *et al*[7], 2010	Ⅱ/26	Ipilimumab	Pancreatic adenocarcinoma	Pretreated	0%	1/26 after progression	NA
Sangro *et al*[16], 2013	Ⅰ/20	Tremelimumab	Advanced hepatocellular carcinoma HCV-induced liver cirrhosis	Pretreated	17.60%	76.40%	NA
El-Khoueiry *et al*[17], 2015	Ⅰ/Ⅱ/41	Nivolumab	Child-Pugh (CP) score ⩽ B7 and progressive disease (PD) on, intolerant of, or refusing sorafenib	77% prior sorafenib	23%	NA	72% at 6m
Bang *et al*[18], 2015	Ⅰb/24	Pembrolizumab	Adenocarcinoma of the gallbladder and biliary tree excluding cancer of the ampulla of vater	⩾ 1 chemotherapy and 38% ⩾ 3	17%	17%	NA
Colon cancer							
Chung *et al*[19], 2010	Phase Ⅱ/47	Tremelimumab	Adenocarcinoma of colorectal cancer	Extensive prior chemotherapy	2%	2%	4.8 mo
Topalian *et al*[20], 2012	Ⅰ/17	Nivolumab	Advanced colorectal cancer	Heavily pretreated	1/17	0	NA
Brahmer *et al*[21], 2012	Ⅰ/18	BMS-936559	Advanced colorectal cancer	Pretreated	0%	NA	NA
Le *et al*[8], 2015	Phase Ⅱ	Pembrolizumab	Adenocarcinoma of colorectal carcinoma (MMR proficient versus MMR deficient)	Pretreated	0% *vs* 40%	NA	2.2 mo *vs* NR
Anal cancer							
Ott *et al*[22], 2015	Ⅰb/25	Pembrolizumab	Refractory metastatic squamous cell carcinoma of the anal canal	Prior systemic therapies	20%	40%	NA
Morris *et al*[23], 2016	Ⅱ/39	Nivolumab	Refractory metastatic squamous cell carcinoma of the anal canal	Previously treated, immunotherapy naïve	21%	58%	NA

ORR: Objective response rate; OS: Overall survival; MMR: Mismatch repair; NR: Not reached; NA: Not available.

even in patients with PD-L1 positive tumors[19-21]. Only one heavily pretreated patient presented a remarkable response to nivolumab and this patient was later found to harbour a MMR-deficient CRC. As such, one phase Ⅱ study demonstrated significant RR (40%) in MMR-deficient CRC patients versus 0% in MMR proficient CRC patients treated with pembrolizumab[8]. Therefore, MMR status is now believed to be a valuable predictor of response to anti-PD1 agents, even more valuable than PD-L1 status for that matter. This finding also extends beyond CRC as it highlights the importance of mutational burden as a predictor to ICI response since patients with MMR deficient malignancies tend to have higher rates of intra-tumoral mutations and a subsequent expression of cell surface neo-antigens leading to a more potent immune response.

Anal cancer

A phase Ⅰb trial evaluating pembrolizumab in pretreated squamous cell anal cancer showed response rates of 20% and a stable disease in 40% of patients PDL1 positive tumors[22]. A multi-institutional eETCTN phase Ⅱ

study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal was presented in ASCO 2016 including 37 patients, some of them carrying HIV or hepatitis B or C. The results showed RR of 21% and DCR of 70%; it was not reported more severe adverse events in HIV positive patients[23].

FUTURE PERSPECTIVES

With the express approval of checkpoint inhibitors in different malignancies, these agents will most likely be gain approval for the treatment of some GI malignancies in the very near future.

Anti-CTLA4 agents are unlikely to yield substantial value in the treatment of GI cancers, especially as single agents, because of lacking clinical activity, except of tremelimumab in HCV-induced HCC.

Anti-PD1 agents will soon be considered for the second line treatment of metastatic squamous cell carcinoma of the oesophagus, metastatic gastric adenocarcinoma and advanced cholangiocarcinoma after standard platinum-based therapy. The new molecular classification of gastric adenocarcinoma will help better define patients that might benefit from these therapies, mainly those expressing PDL1 and EBV positive gastric adenocarcinomas. Anti-PD1 agents will also be considered as second line treatment in advanced HCC while viral hepatitis status should be considered as a predictive biomarker for response since it clearly does not prevent the use of ICI.

Moreover, anti-PD1 agents will most likely be approved MMR-deficient CRC, which represent 10% to 15% of these tumors. Second line treatment of metastatic anal squamous cell carcinoma will also benefit from the emergence of these new agents after standard therapy, and HPV status should be looked into as a predictive biomarker.

With the increasing popularity of chemo-immuno-therapy, it is also likely that such combinations will soon emerge and hasten the approval process in first line settings[24].

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