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ORIGINAL ARTICLE

Efficacy and safety of preoperative immunotherapy alone followed by surgery in the treatment of advanced gastric cancer with MSI-H/dMMR or EBV-positive

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Abstract

Background: At present, there is no consensus on whether preoperative immunotherapy (PIT) without chemotherapy followed by surgery could benefit patients with advanced gastric cancer (AGC). Here, we report a six-case series study to describe the safety and efficacy of PIT plus gastrectomy in patients with AGC.

Methods: This study involved six patients with AGC who received PIT and surgery at our center between January 2019 and July 2021. Demographic characteristics, preoperative gastroscope biopsy pathology, surgical tissue pathology, radicalness of tumor resection, surgical safety, and recovery parameters were reported.

Results: Six patients, including four patients with Epstein-Barr virus (EBV)-positive gastric cancer (GC) and two patients with microsatellite instability-high (MSI-H)/expression deficiency of mismatch repair (dMMR) protein GC, were enrolled in this study. Four patients experienced immunotherapy-related adverse events (irAEs), without severe adverse events (SAEs). Five patients underwent R0 resection, and one patient underwent palliative gastrectomy due to liver and hilar lymph node metastasis. Pathologic responses from the surgical tissue were observed in all patients, including two pathological complete response (pCR). No operative complications or postoperative deaths occurred. Three patients (50%) experienced mild or moderate postoperative complications without severe postoperative complications. All six patients eventually recovered and were discharged.

Conclusion: This study indicated that PIT was effective and tolerant in some patients with MSI-H/dMMR and/or EBV-positive AGC. PIT followed by gastrectomy might be an alternative treatment option for these selected patients.

Keywords: Advanced gastric cancer; EBV-positive; Efficacy; Immunotherapy; MSI-H/dMMR; Safety; Surgery

1. INTRODUCTION

Gastric cancer (GC) is one of the most common malignant tumors of the digestive system in China.[1,2] Most GC patients in China are advanced gastric cancers (AGCs).[2] The treatment of AGC is still a major challenge due to the high risk of recurrence and metastasis. Cancer immunotherapy, as a novel treatment for malignant tumors, has made remarkable progress in recent years and was rated as the first scientific breakthrough in 2013 by Science magazine.[3] Several immune checkpoint inhibitors (ICIs), such as programmed death 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors, which are important parts of cancer immunotherapy, have been approved for the treatment of metastatic or unresectable GC by the U.S. Food and Drug Administration (FDA) and China National Medical Products Administration (NMPA) based on previous studies, including KEYNOTE-059 and ATTRACTION-2 (ONO-4538-12) studies.[4–6]

Although immunotherapy has achieved remarkable success for the treatment of unresectable or metastatic GC, few studies have reported the application of immunotherapy in patients with AGC preparing for surgery. There were just two case reports showing that gastrectomy after preoperative immunotherapy (PIT) for the treatment of AGC had good efficacy and safety.[7,8] Whether patients with AGCs before surgery could benefit from a therapeutic model of PIT plus surgery was undefined. The above remarkable progress in immunotherapy in unresectable or metastatic gastrointestinal malignancies encourages us to probe the application of PIT alone in patients with AGC preparing for surgery. Herein, we presented this six-case series study to assess the safety and efficacy of PIT without chemotherapy followed by surgery in AGC.

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2. METHODS

This case-series study enrolled consecutive AGC patients who received immunotherapy without chemotherapy before gastrectomy at Peking University Cancer Hospital Gastrointestinal Cancer Center I between January 2019 and July 2021. Information including demographics, clinicopathological characteristics, operative parameters, and postoperative recovery parameters was recorded and collected from all reported cases. Demographics included age, sex, body mass index (BMI), comorbidities, abdominal surgery, and American Society of Anesthesiology (ASA) scores. Enhanced abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) were conducted to assess the immunotherapy response based on the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.[9] cTNM, ycTNM, and ypTNM were recorded according to the 8th edition of the Union for International Cancer Control (UICC) tumor-node-metastasis classification.[10] Tumor regression grade (TRG) was also used to assess the response to preoperative immunotherapy according to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology for gastric cancer (version v3.2015, USA).[11] Immunohistochemical (IHC) staining or in situ hybridization (ISH) analysis was performed to determine the expression status of human epidermal growth factor receptor-2 (HER-2), epidermal growth factor receptor (EGFR), PD-L1, mismatch repair (MMR) protein, and EBV status for each surgical tissue specimen and/or gastroscope biopsy specimen. Operative parameters, including surgical approaches, the extent of gastrectomy, anastomosis type, the extent of lymph node dissection, the length of incision, operation time, and estimated blood loss, were collected. Postoperative recovery-related indicators, including first time to aerofluxus, first time to defecation, first time to liquid diet, first time to drinking, first time of getting out of bed, time to drainage tube removal completely, and length of hospital stay after surgery, were collected. The visual analog scale (VAS)[12,13] was recorded to evaluate postoperative pain intensity at 24, 48, and 72 hours after surgery. The time of intravenous patient-controlled analgesia (IV-PCA) and supplementary analgesic dose were collected to assess postoperative pain intensity. The supplementary analgesic dose was converted to oral morphine equivalents (OME) according to opioid oral morphine milligram equivalent (MME) conversion factors.[14] Postoperative complications were defined as complications that occurred during their hospital stay after surgery and were classified and graded by the Clavien-Dindo classification system.[15,16] Postoperative death was defined as death occurring within 30 days after initial surgery regardless of cause. The study was approved by the Ethics Committee of Peking University Cancer Hospital (No. 2018YW118).

3. RESULTS

3.1. Demographic characteristics

In this study, we reported six patients, including five males and one female, who were treated with ICIs, one of the immunotherapy methods (Table 1). Among the patients, two patients were less than 70 years old, and four patients were older than or equal to 70 years old. One patient was overweight (BMI ranging from 25 to 29.9), and five patients were normal weight (BMI ranging from 18.5 to 24.9) based on World Health Organization (WHO) BMI criteria.[17] Two patients were diagnosed with gastroesophageal junction adenocarcinoma, and both of them were Siewert type II according to the Siewert classification system.[10,18] The other four patients' tumor locations were in the gastric fundus, gastric body and antrum junction, gastric fundus and body junction, and gastric angle. The detailed information was listed in the Table 1.

3.2. Gastroscope biopsy pathology and immunohistochemistry results

All patients were diagnosed with adenocarcinoma according to gastroscope biopsy pathology results. One patient (patient 2) had a mixed-type Lauren classification, and the other five patients had an intestinal-type Lauren classification. Only one patient (patient 2) expressed dMMR protein according to the IHC analysis results. There was one patient (patient 4) who had proficient expression of mismatch repair (pMMR) protein from the IHC analysis, but the gene detection result was microsatellite instability-high (MSI-H) type. EBV-positive GCs were found in the gastroscope biopsy specimens of four patients. Only one patient (patient 4) was HER-2 positive based on gene detection. The detailed results of gastroscope biopsy specimen pathology are presented in Table 2.

3.3. Preoperative immunotherapy regimens

Four patients received a combination regimen of two ICIs. Among these four patients, two patients received nivolumab plus ipilimumab (anti-CTLA-4 monoclonal antibody), and the

Table 1

Demographic and clinical characteristics of reported patients

No.	Age	Gender	BMI	Longitudinal site	Transverse site	Borrmann type (CT scan)	ASA score	ECOG PS	Comorbidities	Abdominal surgery
1	67	Male	23.32	U (gastric fundus)	Greater curvature	II	2	0	No	No
2	70	Female	24.11	L (gastric body and antrum junction)	Greater curvature	II	2	1	Rhinallergosis, degenerative osteoarthropathy	Appendectomy, tubal ligation
3	48	Male	28.09	U (gastric fundus and body junction)	Posterior wall	III	2	0	No	No
4	71	Male	22.86	M (gastric angle)	Lesser curvature	III	2	1	No	Laparoscopic cholecystectomy
5	76	Male	24.01	GEJ Siewert II	Posterior wall, anterior wall, and lesser curvature	III	2	1	No	No
6	75	Male	21.76	GEJ Siewert II	Posterior wall and lesser curvature	III	2	1	BPH, right hand tremble	No

ASA = American Society of Anesthesiology; BMI = body mass index; BPH = Benign prostatic hyperplasia; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status GEJ = gastroesophageal junction; L = Lower; M= Middle; U = upper.

Table 2

Gastroscope biopsy pathology, immunohistochemistry, and gene detection results

No.	Pathology type	Tumor differentiation	Lauren type	MMR protein	MSI status	HER2	PD-L1	EBV	TMB	EGFR	Mutations
1	Adenocarcinoma	Poorly differentiated	Intestinal type	MLH1(+), MSH2(+), MSH6(+), PMS2(+)	Missing	0	Tumor cell +50%	Positive	Missing	2+	UGT1A1*6/*28 wild type
2	Adenocarcinoma	Moderately and poorly differentiated	Mixed type	MLH1(−), MSH2(+), MSH6(+), PMS2(−)	MSI-H[c]	No amplification[a]	Missing	Negative	20.0/Mb	Missing	BRCA2 gene frameshift mutation, abundance 6.9%
3	Adenocarcinoma	Poorly differentiated	Intestinal type	MLH1(+), MSH2(+), MSH6(+), PMS2(+)	Missing	0	Missing	Positive	Missing	1+	Missing
4	Adenocarcinoma	Moderately differentiated	Intestinal type	MLH1(+), MSH2(+), MSH6(+), PMS2(+)	MSI-H[c]	Amplification[b]	Missing	Negative	58.87/Mb	3+	UGT1A1*6/*28 wild type, KRAS gene mutation
5	Adenocarcinoma	Poorly differentiated	Intestinal type	MLH1(+), MSH2(+), MSH6(+), PMS2(+)	Missing	1+	Missing	Positive	Missing	2+	UGT1A1*6/*28 wild type
6	Adenocarcinoma	Moderately differentiated	Intestinal type	MLH1(+), MSH2(+), MSH6(+), PMS2(+)	Missing	0	CPS = 80	Positive	Missing	1+	Missing

CPS = Combined positive score; EBV = Epstein-Barr virus; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor-2; MMR = mismatch repair; MSI-H = microsatellite instability-high; PD-L1 = programmed death-ligand 1; TMB = tumor mutational burden.
[a]No amplification: gene detection results.
[b]Amplification: gene detection results.
[c]MSI-H: gene detection results.

other two patients received sintilimab plus ipilimumab. Of the remaining two patients, one patient (patient 4) received toripalimab (anti-PD-1 monoclonal antibody) plus trastuzumab (anti-HER-2 monoclonal antibody) because of HER-2 positive expression, and the other patient (patient 3) received pembrolizumab alone. Only one patient (patient 4) received a cycle of S-1 plus Oxaliplatin (S-1 plus oxaliplatin) before immunotherapy due to severe side effects of chemotherapy converting to immunotherapy. The remaining five patients were untreated with any antitumor drugs before immunotherapy. All six patients were diagnosed with EBV-positive, dMMR or MSI-H GC according to gastroscope biopsy pathology results.

Immunotherapy-related adverse events (irAEs) were found in three patients, and there were no severe adverse events (SAEs), which were defined based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) 5.0.[19] Patient 1 experienced transient fever and immune-related myocarditis. Patient 4 experienced transient fever and shivering when injecting trastuzumab, but transient fever and shivering were not associated with immunotherapy. Patient 5 experienced urinary retention because of immunotherapy. Patient 6 experienced erythra due to immunotherapy.

Two patients achieved partial response (PR), three patients had stable disease (SD), and one patient (patient 5) had progressive disease (PD) according to RECIST 1.1. However, the patient who was regarded as having PD before surgery achieved TRG 2 (fibrosis with scattered tumor cells), according to the surgical tissue specimen pathology. The detailed preoperative immunotherapy regimens, irAEs, and treatment responses are listed in Table 3.

3.4. Surgical and pathological characteristics

Five patients underwent D2 gastrectomy with R0 resection, and one patient (patient 1) underwent palliative distal gastrectomy without lymph node dissection due to hepatic and hilar lymph node metastasis. In this study, three patients underwent total laparoscopic surgery, two patients underwent open surgery, and one patient underwent laparoscopic assistance surgery. Among those who underwent laparoscopic or laparoscopic assistance surgery, conversion from laparoscopic surgery to open surgery occurred in one patient because laparoscopic esophagojejunostomy with a straight-line stapler was difficult. Patient 1 underwent Billroth-I reconstruction. Patient 2 underwent distal gastrectomy with uncut Roux-en-Y reconstruction. Three patients (patient 3, patient 4, and patient 5) underwent total gastrectomy with Roux-en-Y reconstructions. Patient 6 underwent proximal gastrectomy with esophagogastric anastomosis using transorally inserted anvil (Orvil) reconstruction. There were no patients who underwent combined visceral resection in the present study. Two patients achieved pathological complete response (pCR) according to surgical tissue specimen pathological assessments. The detailed surgical and pathological characteristics are listed in Tables 4–6.

3.5. Postoperative complications and postoperative recovery parameters

No complications occurred during the operation, and no postoperative deaths occurred in any of these six patients. Three patients (patient 4, patient 5, and patient 6) experienced postoperative complications, accounting for 50% of all enrolled patients. Patient 4 was diagnosed with pneumonia and pleural effusion through chest X-ray at the bed side on postoperative day (POD) 2. He was treated with ertapenem antibiotics for 5 days and finally recovered. Patient 5 was diagnosed with anastomotic leakage on POD 7 by observing drainage fluid and was kept with draining. Patient 6 occurred transient fever on POD 13. The doctor on duty removed the central venous catheter

Table 3

Immunotherapy regimens, irAEs, and treatment responses of preoperative therapy

No.	Immunotherapy regimens	Neoadjuvant immunotherapy scheme	Immunotherapy cycle	cTNM	ycTNM	Response evaluation based on the RECIST v1.1	irAEs	Time to surgery after immunotherapy ending (d)	Previous treatment lines	Previous treatment regimen
1	Nivolumab and ipilimumab	Nivolumab 64 mg d1, ipilimumab 192 mg d1, q3w (cycle 1); nivolumab 59 mg d1, Ipilimumab 177 mg d1 (cycle 2-3), nivolumab 100 mg d1, q3w (cycle 4-6)	6	cT4aN1M1 H1[a] Hilar lymph node metastasis	ycT2N0M1 H1 Hilar lymph node metastasis	PR	Fever, immune-related myocarditis	63	No	No
2	Nivolumab and ipilimumab	Nivolumab 200 mg d1 q2w (cycle 1); nivolumab 200 mg d1 q2w, ipilimumab 50 mg d1 q3w (cycle 2); nivolumab 200 mg d1 q2w (cycle 3-4)	4	cT4aN3M1 16LNM possible	ycT3N2M0	PR	No	7	No	No
3	Pembrolizumab	Pembrolizumab 200 mg d1 q3w (cycle 1-3)	3	NA	ycT4aN1M0	SD	No	10	No	No
4	Toripalimab and trastuzumab	Toripalimab 240 mg d1 q3w, trastuzumab 0.44 g d1 q3w (cycle 1-9)	9	cT4aN2MxH1? Lung M?	ycT3N2M0	SD	Fever, shivering (because of trastuzumab)	76	1	SOX*1, because of SAE
5	Sintilimab and IBI310	Sintilimab 200 mg d1 q3w+ IBI310 63 mg d1 q6w (cycle 1); sintilimab 200 mg d1 q3w (cycle 2); sintilimab 200 mg d1 q3w+ IBI310 63 mg d1 q6w (cycle 3)	3	cT3N1M0	ycT3N1M0	PD	Urinary retention	17	No	No
6	Sintilimab and IBI310	Sintilimab 174 mg d1 q3w+IBI310 58 mg d1 q6w (cycle 1); sintilimab 171 mg d1 q3w (cycle 2); sintilimab 200 mg d1 q3w+IBI310 58 mg d1 q3w (cycle 3)	3	cT3N1M0	ycT3N1M0	SD	Erythra	22	No	No

irAEs = immunotherapy-related adverse events; NA = Not applicable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = severe adverse event; SD = stable disease; SOX = s-1 plus oxaliplatin; TNM = tumor-node-metastasis.

[a]H1: hepatic metastasis.

Table 4

Surgical parameters of the enrolled patients

No.	Surgical approach	Resection extent	Extent of lymph node dissection	Anastomosis type	Estimated blood loss (mL)	Operation time (min)	Combined organ resection	Length of incision (cm)
1	Laparoscopic	Partial gastrectomy	No	Billroth-I	5	53	No	2
2	Open	Distal gastrectomy	D2 lymph node dissection	Uncut Roux-en-Y	100	200	No	25
3	Laparoscopic	Total gastrectomy	D2 lymph node dissection	Roux-en-Y	100	262	No	5
4	Laparoscopic conversion to open[a]	Total gastrectomy	D2 lymph node dissection	Roux-en-Y	100	238	No	20
5	Open	Total gastrectomy	D2 lymph node dissection	Roux-en-Y	100	247	No	22
6	Laparoscopic assistance	Proximal gastrectomy	D2 lymph node dissection	Esophagogastric anastomosis (Orvil)	50	260	No	8

[a]Laparoscopic conversion to open: laparoscopic esophagojejunostomy with linear cutting closure device was difficult.

(CVC) immediately and treated it with lysine aspirin to bring down the temperature. All these three patients finally recovered. The mean postoperative hospital stay time was 14.7 days (range, 5-24 days). All patients used IV-PCA after the surgery. The detailed postoperative complications and postoperative recovery information are presented in Tables 7–9.

4. DISCUSSION

With the development of immunotherapy in GC, we reported this six-case series study to explore the efficacy of PIT followed by gastrectomy used for treating patients with resectable or potentially resectable AGC. Among the six patients in this study, two patients were diagnosed with MSI-H GCs (including one pMMR), and the other four patients were diagnosed with EBV-positive GCs. All patients responded to immunotherapy according to surgical tissue TRG results.

At present, how to select effective biomarkers for AGC is still a major problem in immunotherapy. There was a lack of enough biomarkers to guide immunotherapy for AGC. MSI-H was regarded as a subtype of GC by The Cancer Genome Atlas (TCGA) in 2014.[20] A previous meta-analysis showed that

Table 5

Surgical radicalness of patients

No.	Proximal margin(cm)	Distal margin(cm)	The number of retrieved LNs	The number of metastatic LNs	Retrieved LNs of No. 1-6	Metastatic LNs of No. 1-6	Retrieved LNs of No. 7-9	Metastatic LNs of No. 7-9	Retrieved LNs of No. 11, 12a	Metastatic LNs of No. 11, 12a
1	1	3	2	0	2	0	0	0	0	0
2	8	7	43	0	24	0	12	0	7	0
3	5	15	51	5	39	5	8	0	4	0
4	1	4	51	0	37	0	11	0	3	0
5	0	15	18[a]	7[a]	8	2	6	2	3	2
6	4	5	26	0	18	0	6	0	2	0

LN = lymph node.

[a]18 and 7: Including one metastatic lymph node in No. 20 station.

Table 6

Surgical tissues pathologic characteristics of patients

No.	Pathology type	Tumor differentiation degree	Long-axis diameter[a]	Short-axis diameter[a]	Borrmann type[a]	Lauren type	ypTNM	TRG	Intravascular cancer emboli	Perineuronal invasion	EGFR	MMR protein	KI67	HER2 result	PD-L1 result	Cmet	EBER
1	Adenocarcinoma	Residual invasive adenocarcinoma	2	1.3	II	Missing	ypT2N0	Grade 2	+	–	Missing	Missing	Missing	Missing	Missing	Missing	Missing
2	pCR	pCR	0.8	0.8	pCR	pCR	ypT0N0	Grade 0	–	–	–	–	–	–	–	Missing	–
3	Adenocarcinoma	Poorly differentiated	8	5	III	Diffuse type	ypT4aN2	Grade 3	–	+	0	MLH1(+), MSH2(+), MSH6(+), PMS2(+)	80%+	0	Missing	0	Positive
4	Adenocarcinoma	Moderately differentiated	12	5	III	Intestinal type	ypT3N0	Grade 3	+	–	3+	MLH1(+), MSH2(+), MSH6(+), PMS2(+)	+75%	2+	CPS = 9	2+	Negative
5	Adenocarcinoma	Poorly differentiated	6	5	III	Mixed type	ypT3N3a	Grade 2	+	+	2+	MLH1(+), MSH2(+), MSH6(+), PMS2(+)	+70%	1+	CPS = 25	1+	Positive
6	pCR	pCR	2	2	pCR	pCR	ypT0N0	Grade 0	–	–	–	–	–	–	–	–	–

EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor-2; Ki-67 = nuclear protein that is associated with cellular proliferation and ribosomal RNA transcription; MMR = mismatch repair; pCR = pathological complete response; PD-L1 = programmed death-ligand 1; TNM = tumor-node-metastasis; TRG = tumor regression grade.

[a]Long-axis diameter, short-axis diameter, Borrmann type: postoperative fresh specimen.

Table 7

Operative and postoperative complications in all patients

No.	Operative complications	Postoperative complication	Diagnostic time (days after surgery)	Complication classification (The Clavien-Dindo classification)	Measures	Outcomes
1	No	No	NA	NA	NA	NA
2	No	No	NA	NA	NA	NA
3	No	No	NA	NA	NA	NA
4	No	Pneumonia, pleural effusion	POD 2	Grade II	Treatment with ertapenem antibiotics	Recovery
5	No	Anastomotic leakage	POD 7	Grade I	Drainage and observation	Recovery
6	No	Transient fever	POD 13	Grade II	Pulling up CVC and treatment with lysine aspirin	Recovery

CVC = central venous catheter; NA = not applicable; POD = postoperative day.

patients with MSI-H AGC could not benefit from the addition of chemotherapy to surgery.[21] The KEYNOTE-177 study showed that patients with unresectable and metastatic MSI-H colorectal cancer (CRC) could benefit from immunotherapy.[22] Further analysis of the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials showed that MSI-H GC patients could have a better response to immunotherapy than patients with microsatellite stability (MSS) GCs.[23] In addition, a previous

Table 8

Postoperative recovery parameters of patients

No.	The first aerofluxus time (d)	The first defecating time (d)	The first time to drinking (d)	The first time of getting out of bed (d)	The first time on liquid diets (d)	Time to pull gastric tube (d)	Number of drainage tubes	Time to pull drainage (d)	Length of stay (d)
1	1	2	1	1	2	…[a]	0	…[a]	5
2	3	4	1	1	4	…[a]	1	7	9
3	2	2	2	1	3	2	2	7	19
4	4	4	1	1	4	9	2	8	13
5	5	5	2	1	5	20	3	20	24
6	5	5	4	3	5	…[a]	1	6	18

[a]No gastric tube or drainage tube were placed during the operation.

Table 9

Subjective evaluation of acute pain intensity, IV-PCA, and supplementary morphine consumption after surgery

No.	Postoperative pain at 24 h (VAS)	Postoperative pain at 48 h (VAS)	Postoperative pain at 72 h (VAS)	Using IV-PCA	Time of using IV-PCA (d)	Supplementary morphine consumption (mg)
1	0	0	0	Yes	4	0
2	4	0	6	Yes	4	30.24
3	6	6	0	Yes	6	80
4	0	0	0	Yes	3	0
5	0	0	6	Yes	2	80.48
6	0	0	0	Yes	4	0

IV-PCA = intravenous patient-controlled analgesia; VAS = visual analog scale.

case-series study reported that PIT could result in favorable pathological responses and minor adverse effects among patients with MSI-H GCs and MSI-H CRCs without compromising subsequent surgery.[8] EBV-positive GC is another subset of GC with unique genomic aberrations and significant clinicopathological features, accounting for 8.8% of all GCs according to a previous study.[20] A previous study showed that EBV-positive GC had high expression of immune checkpoint pathways (PD-1 and CTLA-4 pathways) and immune infiltration.[24] Moreover, several studies have indicated that EBV-positive GC could benefit from immunotherapy.[25–27] All these studies indicated that MSI-H or EBV positivity was an effective biomarker for predicting the efficacy of immunotherapy. The results of this study also suggested that patients with MSI-H or EBV-positive GCs could possibly benefit from PIT. Perhaps for these selected patients, single-agent immunotherapy was an option beneficial to them.

Currently, the standard treatment to be recommended in clinical practice for cStage III is D2 gastrectomy with perioperative chemotherapy.[28] In this study, these six patients were treated with PIT followed by gastrectomy without chemotherapy due to the following results. The regimen of patient 4 was converted from chemotherapy to immunotherapy because SAE occurred during the first chemotherapy cycle. Three patients (patients 2, 5, and 6) in this study were over 70 years old with poor physical strength, Eastern Cooperative Oncology Group performance status (ECOG PS) 1. Generally, elderly patients were less able to tolerate chemotherapy.[29] Previous studies showed that patients with MSI-H GC could benefit more from immunotherapy than from chemotherapy with fewer side effects than immunotherapy plus chemotherapy or chemotherapy.[30] Based on the above considerations, these four patients and their families decided to participate in clinical trials and were treated with immunotherapy. Similarly, two EBV-positive patients (patient 1 and patient 3) received immunotherapy alone after a detailed explanation of the immunotherapy benefit.

All these patients were tolerant to the PIT. Four patients experienced mild and moderate irAEs. No SAE or immunotherapy-related death was reported in the study. According to the review reported in The New England Journal of Medicine (NEJM), immune checkpoint blockade can have inflammatory side effects termed immune-related adverse events. Any organ system could be affected, and irAEs most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver.[31] However, unlike immunotherapy for unresectable or metastatic GCs, ir-AEs, especially ir-SAE, could have an impact on surgery, which might affect prognosis. PIT must guarantee enough safety and efficacy without immunotherapy-related death or disease progression.

The duration time of PIT ranged from three to nine cycles in this study. Currently, how long the PIT should last remain unclear. A previous study suggested that six cycles of perioperative or postoperative chemotherapy tended to reach the maximum survival benefits in patients with AGC.[32] Whether it was suitable for PIT also remains unknown. Additionally, the time to surgery after PIT ranged from 1 to 9 weeks in this study. A previous study indicated that patients who received surgery within 3-5 weeks after preoperative chemotherapy had the maximal survival benefit.[32] Similarly, there was no consensus on the optimal time to surgery after PIT. Thus, these questions, including how to balance the efficacy and safety, the time to surgery after PIT, and the duration time of PIT, remain to be further researched and addressed in the future.

In this case-series study, three patients (50%) experienced postoperative complications. According to previous studies, the postoperative complication rate of gastrectomy without any preoperative treatment ranges from 3.5% to 52.6%.[33–36] Compared to surgery alone, the postoperative complication rate of PIT was higher but reasonable. Moreover, there were no severe postoperative complications (grade III or above complications based on Clavien-Dindo classification systems). Gastrectomy could be performed safely in patients with AGC who received PIT without increasing the severe postoperative complication rate and surgery-treated death. Four patients underwent surgeries through laparoscopic approaches successfully in this study. This study showed that minimally invasive treatment, such as laparoscopic surgery or laparoscopic assistance surgery after immunotherapy, was feasible and worth further exploration.

In addition, although all these patients received IV-PCA after surgery, three patients received supplementary postoperative analgesics. Among these three patients, two underwent surgeries through open approaches. This result suggested that laparoscopic surgery was less invasive and might be associated with less postoperative analgesic use after surgery in patients with AGC after PIT.

In this study, the result of MMR protein from IHC was inconsistent with MSI-H status from gene detection in patient 4. Previous studies indicated that approximately 10% of colorectal cancer patients with MSI-H status showed pMMR protein expression by the IHC method. Multiplex fluorescent polymerase chain reaction (PCR) is regarded as the gold standard for MSI testing and could cover the disadvantage.[37–39] Compared with the IHC method, PCR detection could not only compensate for the deficiency that IHC cannot detect some MSI-H results but also has good repeatability. However, this method has some disadvantages, such as fewer loci, low flux, inability to provide specific gene mutation information, and long experiment time. Next-generation sequencing (NGS) is another method for MSI testing. NGS is faster and has higher sensitivity and specificity than PCR. However, it is expensive. Thus, for a more precise detection of MSI status, IHC combined with PCR was recommended for MMR/MSI detection when the amount of tissue was enough. In addition, PCR should be considered for one-time detection in the case of limited tissue samples. When more diagnostic information is needed, NGS should be recommended.

In addition, the response evaluation of PIT in patient 5 was PD based on the preoperative enhanced abdominal CT scan according to RECIST 1.1 criteria, which was not in accordance with the surgical tissue specimen pathological results. Until now, there has been no universally recognized standard for immunotherapy response. In the present study, RECIST 1.1 was used to assess the PIT response according to clinical practice, which has been widely accepted in evaluating patients receiving chemotherapy in GC. However, there were major challenges in assessing the tumor response to immunotherapy by RECISST 1.1 because some response types, such as dissociative response or pseudoprogression, may not be accurately identified.[40,41] The dissociative response pattern was defined as enlargement in the size of some lesions and a reduction in other disease sites simultaneously.[41,42] Pseudoprogression was defined as the target lesion continuing to grow or the appearance of new lesions followed by shrinkage of tumoral lesions. This enlargement might be led by stimulating the immune system by hyperactivated T cells.[42,43] Patient 5 might belong to this scenario. For this case, the treatment was terminated early due to mistakenly considering that PIT was not effective. Because of these limitations of RECIST 1.1 for immunotherapy response, several new response criteria, such as immune-related response criteria (irRC), immune-related RECIST (irRECIST), and immune-RECIST (iRECIST) guidelines, were developed for immunotherapy response assessment.[41,44–46] Although these new methods were rational approaches regarding the immunotherapy response, they were still not validated by prospective studies and are not widely accepted for application in PIT response in GC. In addition, enhanced abdominal CT scans sometimes cannot distinguish between fibrosis and residual tumors. Histopathological analysis was considered the gold standard, but the results could not be known before the surgery. Positron emission tomography (PET)/CT might be a promising tool because tissue density signal changes and metabolic changes in the tumor could be identified by PET/CT compared with traditional anatomical imaging modalities. Thus, to assess the PIT response exactly, new response criteria and new imaging modalities such as PET/CT should be considered for PIT response assessment in GC.

There were some limitations in this study. Obviously, this was a case-series study, which provided low-level evidence according to the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence system.[47,48] Second, this is a single-arm study with a small and limited sample size. Thus, it is difficult to generalize our findings to other patients. Third, there were some missing data in some cases. Last, although all these patients in this study responded to PIT, whether there were patients with MSI-H or EBV-positive AGC who were refractory to immunotherapy remains unclear. As a biomarker of immunotherapy, the sensitivity and specificity of MSI-H and/or EBV positivity in AGC are undefined. Further studies are needed to validate the efficacy of PIT in patients with MSI-H or EBV-positive AGC.

In conclusion, this study indicated that PIT was effective and tolerant to some patients with MSI-H/dMMR or EBV-positive AGC before surgery. PIT followed by gastrectomy might be an alternative treatment option for these selected patients. Further studies are needed to confirm it.

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