Case Report

Response to the rechallenge of combination immunotherapy in a patient with late-stage gastric cancer: case report

Zhening Zhang, Siyuan Cheng, Changsong Qi, Xiaotian Zhang, Zhi Peng, Lin Shen

Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research, Peking University Cancer Hospital & Institute, Beijing, China

Correspondence to: Zhi Peng. No.52, Fucheng Road, Haidian District, Beijing 100142, China. Email: zhipeng3@hotmail.com.

Abstract: Until present, late-stage gastric cancer (GC) remains a refractory disease featured with poor prognosis. However, the upcoming era of immunotherapy turns situations around. Programmed death-1 receptor (PD-1)/programmed death-ligand 1 (PD-L1) signaling blockade, an option of immune checkpoint inhibitor (ICI), has gained approval for the third-line treatment of patients with locally advanced and/or metastatic GC. Despite its efficacy in a few tumor subtypes, most patients are insensitive to anti-PD-1 monotherapy. Therefore, growing interests arise in combination immunotherapy. To explore the maximal potentials of ICI, oncologists also focus on ICI rechallenge. Here we present a patient with unresected stage IV, Epstein-Barr virus (EBV) unrelated, microsatellite stable and HER2 heterogeneously expressed gastric adenocarcinoma who experienced the failures of previous immunotherapy. He was then rechallenged with identical ICI regime combined with tyrosine kinase inhibiting and anti-HER2 therapy. The patient responded and tolerated well to this regimen and survived with fair living quality after 28 months of treatment. This case suggests that patients who fail frontline immunotherapy still possibly benefit from rechallenge of the same anti-PD-1 regimen. Besides, combination of ICI and other target agents might intrigue a synergistic effect, resulting in enhanced anti-tumor effect, which provides a meaningful therapeutic strategy. Relevant studies are underway of investigation and might be a hotspot for future research.

Keywords: Gastric cancer (GC); immunotherapy; immune checkpoint inhibitor (ICI); rechallenge; combination therapy; case report

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Introduction

Gastric cancer (GC) is the fifth most common cancer with over 1,000,000 new cases annually, and also the third leading cause of cancer mortality worldwide (1). Despite that interventional endoscopic therapy or surgeries make early-stage GC curable, many late-stage patients have already been subject to local advancement and/or metastasis (stage IV) at diagnosis, losing chances of radical therapy (2,3). Traditionally, multiline sequential chemotherapy is the standard treatment principle for unresectable late-stage GC patients (4).

The marvelous discovery of immune checkpoints has revolutionized the field of cancer therapeutics. Programmed death-1 receptor (PD-1) and its ligands (PD-L1/PD-L2) are a pair of immunosuppressive molecules whose interactions downregulate T cell function. Previous studies have shed light on the important roles of PD-1/PD-L1 signaling during tumorigenesis (5). Immune checkpoint inhibitor (ICI) could efficaciously rescue anergic immune cells and restart the host anti-tumor immune response. Pembrolizumab (Keytruda) and nivolumab (Opdivo) are two anti-PD-1 monoclonal antibodies which have gained approval for the third-line treatment of locally advanced and/or metastatic GC patients due to the encouraging results of Keynote-059 and Attraction-2 (2,3). Current evidence indicated that Epstein-Barr virus (EBV)-related, mismatch repair (MMR) deficient or PD-L1 highly expressed GC have better response to immunotherapy in

contrast to other subtypes in terms of overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) (6,7). However, these populations only make up a small portion of late-stage GC patients. Pembrolizumab monotherapy failed to improve OS compared with optimal chemotherapy in the frontline therapy for most patients, according to the results of Keynote-061 and Keynote-062 (8,9). In that case, many questions remain undefined. First, how to expand applicable populations of ICI? Second, what are subsequent treatment options after the initial failure of ICI monotherapy? During recent years, the strategy of combination immunotherapy has been put forward, providing options to break the current dilemmas. The efficacy of combination immunotherapy in GC patients should be examined. Besides, though ICI rechallenge has been reported in other cancer types, it has never been discussed in the field of GC among past literature.

Herein, we reported the case of a male patient who developed stage IV gastric adenocarcinoma, got progressed on immunotherapy and was then rechallenged with the combinations of pembrolizumab, anlotinib, trastuzumab and ultimately attained a continuous response. We present the following case in accordance with the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-83/rc).

Case presentation

A 60-year-old male patient presented in April 2017 with a liver mass during a routine medical examination. When admitted into our hospital, he was asymptomatic except for inconspicuous body weight loss. His past medical history was uneventful. The patient completed a liver mass biopsy and the result suggested a malignant gastrointestinal origin. The patient then undertook gastroscopy and a positron emission tomography-computed tomography (PET-CT) scan, which indicated enhanced metabolism in the lesser curvature of the stomach. According to the imaging and histological evidence, he was diagnosed with moderately differentiated gastric adenocarcinoma with isolated liver metastasis (*Figure 1*). The clinical and molecular information of this patient is summarized in *Table 1*.

He initially received 6 cycles of XELOX (oxaliplatin 200 mg day 1, capecitabine 1,500 mg bid day 1–14) and trastuzumab (Herceptin 440 mg day 1) since June 2017. According to the response evaluation criteria in solid tumors (RECIST 1.1), the patient was evaluated as radiologic stable disease (SD), SD and progressive disease (PD) after 2, 4 and 6 cycles of treatment, respectively. He discontinued therapies and got discharged. 2 months later, he was enrolled in the trial *A Phase Ia/Ib Study of CS1001 in Subjects with Advanced Solid Tumors* (NCT03312842) and initiated 2 cycles of anti-PD-L1 therapy (CS1001, 610 mg day 1). Nevertheless, he was soon out of the trial due to severe gastrointestinal bleeding. 4 weeks later, the patient was re-admitted and received S-1 (60 mg bid day 1–5, 8–12, 15–19) and synchronous irradiation of the gastric lesion (95% PGTV 50 Gy/95% PTV, 45 Gy/25 f). Five months later, a restaging computed tomography (CT) scan indicated enlarged peri-gastric lymph nodes which demonstrated PD. He accordingly adjusted the regimen to paclitaxel (270 mg day 1) and S-1 (60 mg bid day 1–14). Two cycles later, he was evaluated as SD but developed grade 3 neuropathy which impaired his life quality. Therefore, docetaxel (100 mg day 1) was commenced in place of paclitaxel. He was evaluated as SD following 4 cycles of treatment. During cycle 5, he developed grade 2 diarrhea and then discontinued docetaxel. One week later, the restaging CT revealed new-onset nodules in the retroperitoneum, pelvic cavity, residual liver and lung, which demonstrated PD. The patient then changed regimen to irinotecan (249 mg day 1). One week later, the chest CT scan revealed an enlarged pulmonary nodule, and the abdominal and pelvic CT scan demonstrated an increased density of peritoneum and omentum majus. He was evaluated as PD again and got discharged. One month later, he was administrated with 2 cycles of CDK4/6 inhibitor (Palbociclib, 125 mg day 1–21) in combination with pembrolizumab (Keytruda, 200 mg day 1) but got limited response. Considering the patient's strong desires and restricted options for further-line therapies, we treated him actively with 5 cycles of anlotinib (12 mg day 1–14), trastuzumab (Herceptin, 440 mg day 1) and pembrolizumab (Keytruda, 200 mg day 1). He responded rapidly and was assessed as a radiologic partial response (PR) after 4 cycles of treatment (*Figure 2*). He developed grade 3 oral mucositis requiring anlotinib reduced to 12 mg 2 doses every 3 days, and the symptom relieved within days. He presented durable responses and well tolerance to two further cycles of treatment. Until present, the patient only suffers grade I numbness of bilateral lower limbs without treatment interruption. He is alive with acceptable living quality for over 2 years since the initial diagnosis, and thus far the combination immunotherapy is ongoing. Complete treatment timeline is presented in *Figure 3*. Tumor markers are also monitored

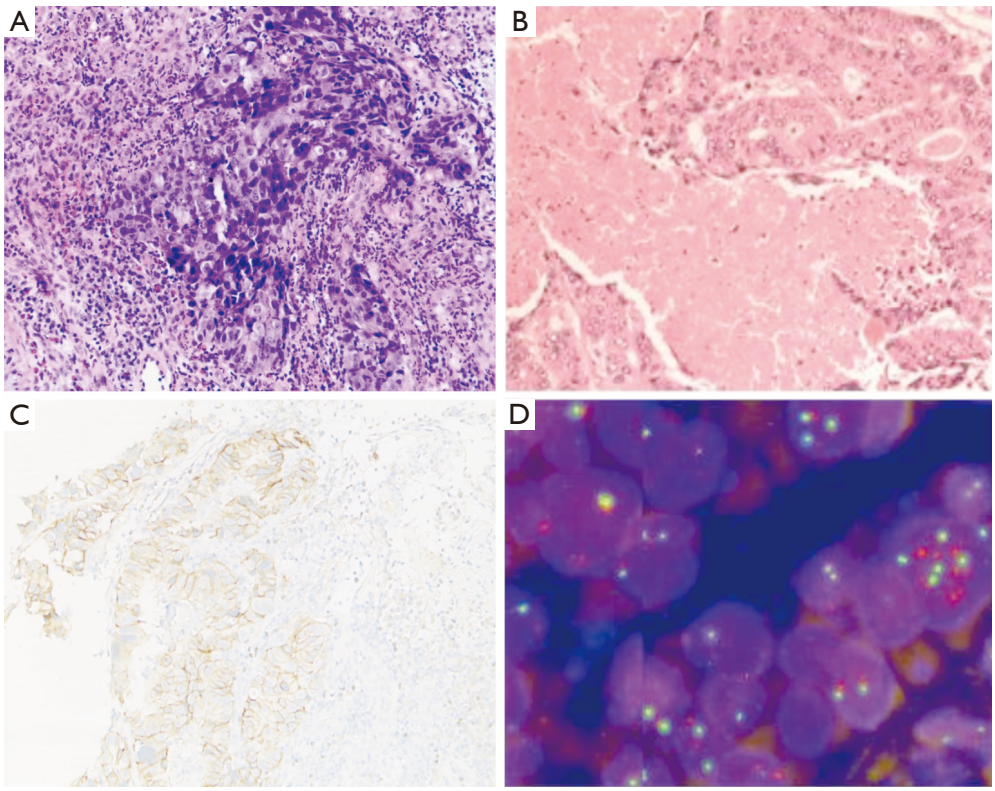

Figure 1 Pathologic results of the liver mass biopsy. (A) The low-medium differentiated adenocarcinoma, in which most glands were poorly structured. (H&E staining, original magnification was ×100). (B) The biopsy indicated that it was a metastasis coming from the stomach based on morphological and molecular evidence. (H&E staining, original magnification was ×100). (C) Negative PD-L1 staining in tumor cells. (IHC staining, original magnification ×100). (D) Negative HER2 amplification detected by FISH. PD-L1, programmed death ligand-1; FISH, fluorescence in situ hybridization.

during the whole process of therapy (*Figure 4*).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In this report, we described a patient with late-stage GC who progressed on multiline therapies including ICI but showed a durable response to the combination of ICI rechallenge, RTKI and anti-HER2 therapy.

Locally advanced/metastatic (stage IV) GC is refractory and has challenged oncologists for years. First-line and second-line therapies have been standardized, resulting in relatively uniform regimens (2,4). In terms of this patient, the sequential regimen of oxaliplatin, capecitabine, irinotecan, taxanes and S-1 was adopted. Unfortunately, chemoradiotherapy was inefficacious and elicited severe treatment-related adverse effects (trAEs). We had no choices for evidence-based chemotherapies, therefore anchored hopes on target therapies.

Palbociclib is a highly selective CDK 4/6 inhibitor which arrests cell cycle progression at the G1 phase, thereby plays an anti-tumor role (10). According to the TCGA database, a portion of GC harbor abnormal cell-cycle-related molecules (11). Besides, *in vitro* studies also indicated that certain GC cells are sensitive to cell cycle inhibiting (12,13). These encouraging results drive us to experimentally commence the patient with Palbociclib.

In our case, the combination of trastuzumab, pembrolizumab and anlotinib eventually led to patient's

Table 1 Clinical and molecular information of the patient

Items	Detection method	State/value
Patient-related		
PS	–	1
HP infection	^{13}C-UBT	+
Tumor-related (primary tumor)		
Laurén classification	H&E staining	Intestinal type
TMB	NGS	12.2 mutations/Mb
MSI status	NGS	MSS
EBER expression	IHC	–
PD-L1 expression	IHC	10% positive in tumor cells
EGFR expression	IHC	+
HER2 expression	IHC	++
	FISH	–

PS, performance status score; HP, helicobacter pylori; ^{13}C-UBT, ^{13}C-urea breath test; H&E, Hematoxylin and Eosin; TMB, tumor mutation burden; NGS, next-generation sequencing; MSI, microsatellite instability; MSS, microsatellite stable; EBER, EBV-encoded RNA; IHC, immunohistochemistry; PD-L1, programmed death ligand-1; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; FISH, fluorescence in situ hybridization.

durable responses, based on serological and imaging evidence. It only brought about mild neurological adverse effects to the patient. Notably, this patient was initially insensitive to both immunotherapy and anti-HER2 therapy. More interestingly, anti-angiogenic single therapy only brings about poor response rate among advanced GC patients, and so anlotinib is typically used with other agents. Apparently, the unexpected durable response could not be elicited by either of these three drugs alone. The addition of anlotinib to ICIs is very likely to rejuvenate immunotherapy, which contributes to the success of the rechallenge.

The primary lesion of this patient was tested HER2 negative by FISH, thus was not generally indicated for anti-HER2 treatment due to the result of the ToGA trial (14,15). However, several factors were taken into considerations. First, the patient had previously completed a next-generation sequencing of the liver metastatic biopsy which suggested HER2 amplification. Literatures have reported the discordance of HER2 status between primary and metastatic lesions, which might be attributed to tumor heterogeneity (16,17). Second, the HER2 expression level in a single location could vary along with disease evolution or therapeutic process (17,18). Third, with the advent of new detection strategy, a portion of patients who are initially evaluated HER2 negative still benefit from anti-HER2 therapy (17,19). Therefore, we added trastuzumab into the combination regimen.

The combined administration of anti-PD-1 and anti-HER2 therapy has theoretical and practical foundations. Reportedly, HER2 blockade enhances antibody-dependent cell-mediated cytotoxicity (ADCC) via T cell priming, which has a synergistic effect with anti-PD-1 therapy (20). The 1188 PD study was a nonrandomized, phase II, multicohort trial to evaluate the efficacy and safety of pembrolizumab combined with margetuximab (a more efficient monoclonal antibody targeting HER2) in the treatment of HER2 positive GC after progression on first-line trastuzumab. The combination immunotherapy in this study resulted in a median OS of 12.9 months, longer than previous second-line data (9.6 months in Rainbow and 9.1 months in Keynote-061) (21). Notably, a considerable portion of patients who converted to HER2 negative after receiving trastuzumab still benefited from combination immunotherapy. These results suggest that concurrent anti-PD-1 and anti-HER2 therapy is a robust and efficacious combination strategy.

Anlotinib is a novel small-molecule RTKI which blockades VEGFR-2, PDGFR-β, FGFR-1 and c-Kit, posing a powerful anti-angiogenesis activity (22). Its efficacy and safety in the salvage treatment of solid tumors have been demonstrated by several clinical trials (22,23). The result of phase III ALTER 0303 trial showed that anlotinib monotherapy brought significant benefits in OS (9.6 *vs.* 6.3 months) and PFS (5.4 *vs.* 1.4 months) to patients with advanced non-small cell lung cancer over placebo (24). Recently in a phase I pioneer study, a combination of sintilimab (targeting PD-1) and anlotinib presented favorable efficacy and safety in the first-line therapy of lung cancer (25). In the field of GC, preclinical studies focusing on targeting both VEGFR-2 and PD-1 have also shown promising outcomes (26,27). Considering the current evidence and the promising outcome in our case, we have good reason to assume the extraordinary anti-tumor effect of this combination among GC patients.

Actually, this synergistic effect has been partly elucidated by previous studies. Angiogenesis, featured with aberrant blood vessels formation, is highly related to the progression of cancer and immunoregulation (28).

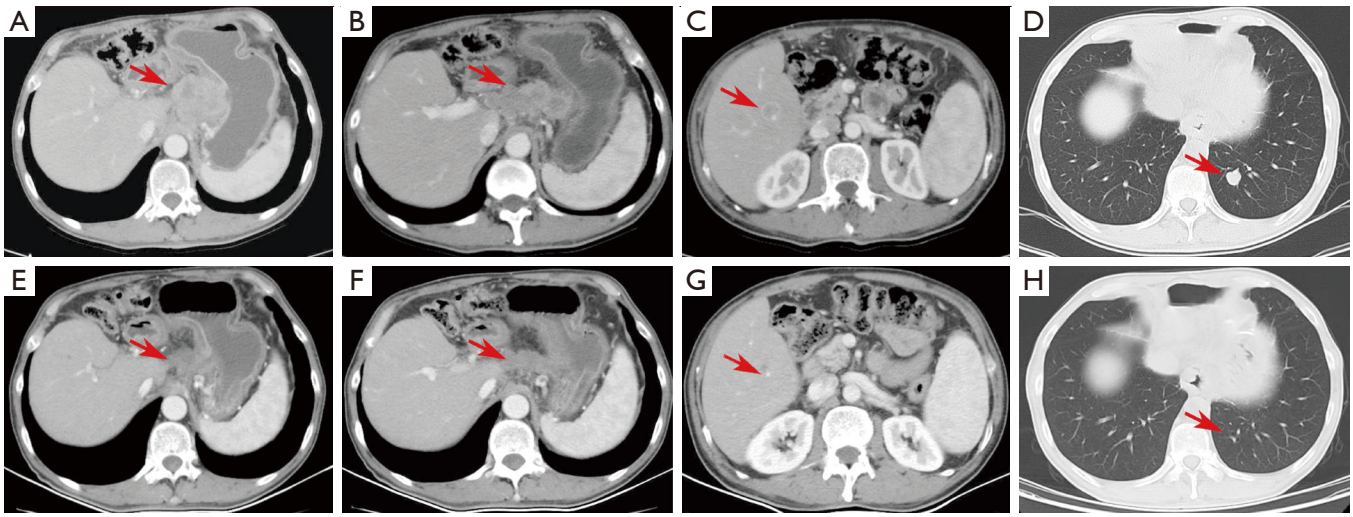

Figure 2 Imaging findings of response after combination immunotherapy. (A) The abdominal CT scan showed a thickening wall of lesser curvature and multiple enlarged peri-gastric lymph nodes (54 mm × 47 mm). (B) Enlarged lymph nodes (28 mm × 28 mm) surrounding the celiac trunk. (C) Isolated intrahepatic nodule (18 mm × 14 mm). (D) Nodules in the lower lobe of the left lung (14 mm × 13 mm). (E) The thickening wall of lesser curvature and peri-gastric lymph nodes shrunk (26 mm × 22 mm). (F) Reduced size of lymph nodes (18 mm × 18 mm) surrounding the celiac trunk. (G) Reduced size of the intrahepatic nodule (7 mm × 5 mm). (H) Nodules in the lower lobe of the left lung grew down to almost disappeared (14 mm × 13 mm). (A) to (D) were generated before combination therapy (2019-4-10); (E) to (H) were generated after 2 cycles of combination immunotherapy (2019-5-28).

Typically, VEGF signaling mediates the immunosuppressive tumor microenvironment (TME) by reducing functional T cell infiltration, inducing and aggregating suppressive immune cells within tumor (29). The administration of anti-angiogenic agents contributes to the normalization and maturation of aberrant blood vessels, which improves vascular permeability and therefore enhances the drug delivery, perfusion and oxygenation of TME (30). As the ameliorative TME facilitates T cell infiltration, ICI further mediates T cell mobilization and activation. In that way, host anti-tumor function could be restored.

Besides the aforementioned combinations (ICI + anti-HER2 or ICI + anti-angiogenesis), other combination strategies have also been explored presently. In the phase II study CheckMate-032, dual pathway ICIs (nivolumab targeting PD-1 and ipilimumab targeting CTLA-4) resulted in an ORR of 24% among advanced/metastatic gastroesophageal cancer patients who had previously treated with ≥1 chemotherapy regimen (31). In the Keynote-062 study, among MSI-H subgroup, patients who received concurrent immunotherapy and chemotherapy indicated significantly higher OS compared with chemotherapy alone (9). So far, evidence of various combination strategies is still insufficient. The optimal combination regimens, potential beneficiaries and the underlying molecular biology theories still need to be addressed in the future.

In the clinical setting, suspension and restart of ICI are also issues worthy of discussing. Treatment resistance and severe trAEs secondary to immunotherapy commonly lead to drug withdrawal. An encouraging fact is that ICI (alone or in combination with other therapies) rechallenge is indeed efficacious in certain situations (32-36). However, little information is known in the field of GC. It might be easier to comprehend the efficacy of ICI resume following adverse-event-related drug withdrawal, while acquired responses in the context of initial treatment failure remain incomprehensible. None of ICI, anlotinib or trastuzumab alone could lead to a favorable response. We speculate that the reversal of immunosuppressive TME mediated by anlotinib and the enhanced ADCC effect mediated by trastuzumab successfully broke the tumor resistance to ICI and therefore contributed to the favorable anti-tumor response.

This case indicates that previously ICI-treated GC patients might regain sensitivity to ICI. It has significant reference value for the clinical management of GC patients.

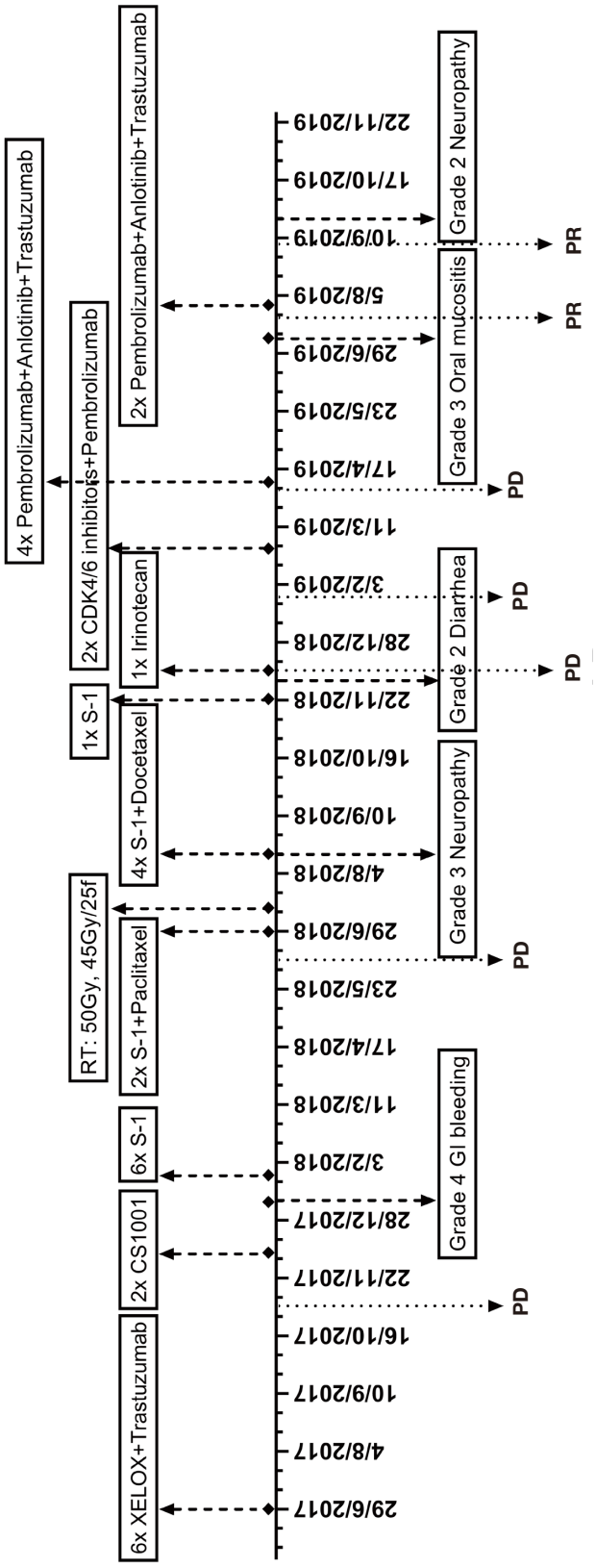

Figure 3 Timeline of the patient's multiline treatments, treatment-related adverse effects and responses. PD, progressive disease; PR, partial response; RT, radiotherapy; GI, gastrointestinal; XELOX, oxaliplatin + capecitabine.

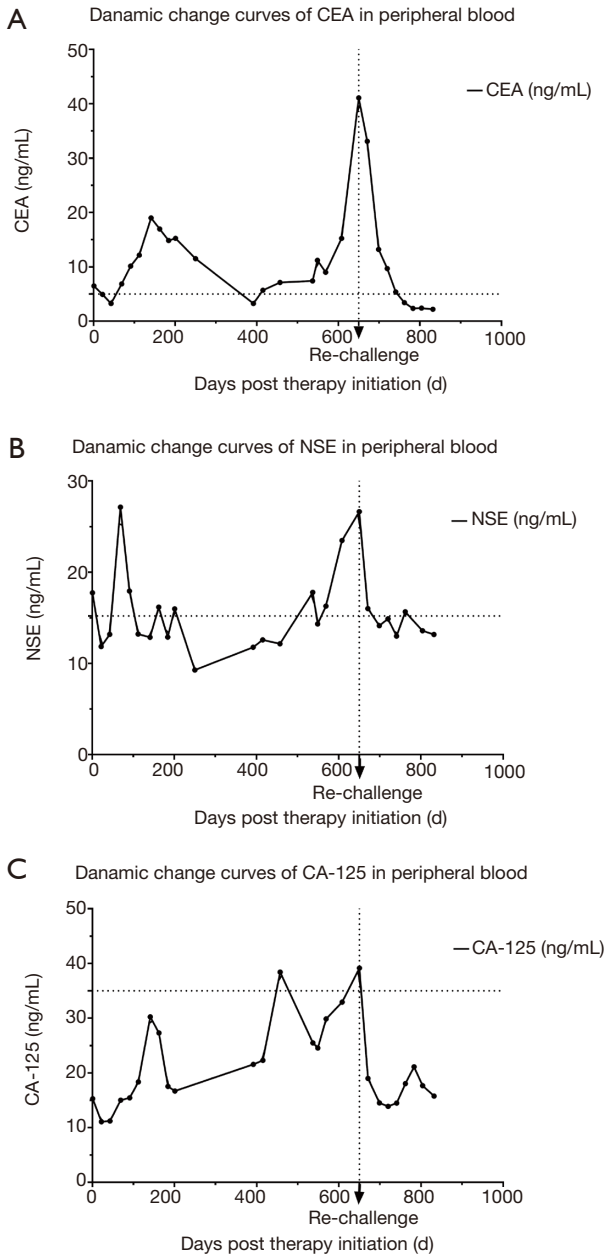

Figure 4 Dynamic change curves of tumor markers in peripheral blood after initiation of multiline treatment. (A) The CEA showed a fluctuation in the related quantity during the previous lines of treatment and peaking when initial ICI regimen failed, followed by a rapid decrease after ICI rechallenge. (B) and (C) The curves of NSE and CA-125 were similar to (A). The horizontal dashed line represented the normal range of tumor markers. Intuitively, tumor markers decreased to a low level and kept within a normal range, which indicated a favorable response. CEA, curves of carcinoembryonic antigen; NSE, neuron-specific enolase; CA-125, carbohydrate antigen-125.

Future investigations should focus on the rationales and applications of combination immunotherapy and ICI rechallenge.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-83/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-83/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article. A copy of the written consent is available for review by the editorial office of this journal.

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