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Letter to the Editor

Effective anti-programmed cell death 1 treatment for chemoresistant gestational trophoblastic neoplasia

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To the Editor,

Gestational trophoblastic neoplasia (GTN) represents a group of rare tumours that account for <1% of all gynaecologic cancers which result from malignant transformation of a trophoblast, a cell that originates from the placenta. Most patients with GTN generally receive standard treatment with traditional single-agent or polychemotherapy regimens, which are known to be effective in achieving 65%–95% successful remission rate. However, these regimens are also associated with high toxicity, and about 5% of patients succumb due to multi-drug resistance [1], necessitating novel therapeutic approaches. Programmed cell death ligand 1 (PD-L1) protects the placenta, which expresses paternal antigens, against maternal immune recognition during pregnancy and maintains gestational tolerance. Recent studies found a strong expression of PD-L1 in GTN [2,3], suggesting that this ligand is involved in tumour-immune evasion. Therefore, targeting programmed cell death 1 (PD-1) inhibitory signalling may be effectual in chemoresistant or refractory GTN. This strategy has been investigated and reported to be very successful in patients with chemoresistant GTN responses, although the numbers are limited [1,4] (Table 1). Based on these results, PD-1/PD-L1 inhibitors have been suggested to

Abbreviations: PSTT, placental site trophoblastic tumour; ETT, epithelioid trophoblastic tumour; PD-L1, programmed cell death ligand 1; MSI, microsatellite instability; hCG, human chorionic gonadotropin; CT, computed tomography; PET, positron-emission tomography; CR, complete remission.

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play a role in treating chemoresistant GTN according to the recent National Comprehensive Cancer Network (NCCN) guidelines. We describe two patients with extremely rare GTN who improved dramatically and were managed by a PD-1 inhibitor.

A 39-year-old woman (Patient 1, parity 1-0-3-1) was diagnosed with placental site trophoblastic tumour (PSTT) via emergent total laparoscopic hysterectomy for uterine rupture in July 2015; the tumour was of stage IV with a World Health Organisation (WHO) prognostic score of 15 points. She had gastrointestinal tract recurrence and continued metastasis despite multi-agent chemotherapy (EMA-CO [etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine] x 13) and had to undergo three more operations (peritoneal mass excision in March 2016, Hartmann operation for rectal infarction with perforation in August 2016 and small bowel resection for perforation in January 2017). The patient continued EMA-EP (etoposide, cisplatin) chemotherapy treatments, undergoing seven sessions after the last operation. Her functional status worsened, and she developed intraperitoneal abscess and infection with bone marrow suppression, which led to further delay in cancer treatment. Immunohistochemistry (IHC) of the tumour component for PD-L1 revealed 100% PD-L1 expression using the 22C3 antibody (Dako, Santa Clara, CA) (Fig. 1-A-①, ②), and the microsatellite instability (MSI) status was determined to be high using multiplex polymerase chain reaction (PCR) with five quasi-monomorphic mononucleotide repeat markers (Fig. 1-B). The β-human chorionic gonadotropin (β-hCG) concentration of this patient had never fallen to normal range while receiving many lines of cytotoxic chemotherapies. The interval between the last EMA-EP chemotherapy and the first pembrolizumab treatment was as long as 4 months, with the β-hCG concentration increasing from 22 to 67 IU/L during the chemotherapy rest period (Fig. 1-C-①), which normalised to less than 5 IU/L after only one cycle of pembrolizumab (200 mg fixed dose, every 3 weeks) (Fig. 1-C-②) and subsequent radiologic complete remission (CR) after four additional cycles (Fig. 1-D-①, ②, ③). In November 2018, after eight more consolidation cycles, it was discontinued. She tolerated the treatment well, without any other symptoms except grade I liver enzyme increase. Currently, the patient remains in a state of CR for more than 5 months. We are planning to reverse the colostomy.

A 49-year-old woman (Patient 2, parity 1-0-1-1) presented with epithelioid trophoblastic tumour (ETT) and vaginal metastasis in July 2012; the tumour was of stage IV with a WHO prognostic score of 14 points. She received numerous cytotoxic, single- or multi-agent, chemotherapies (actinomycin-D x 14, methotrexate x 7, EMA-CO x 14, paclitaxel-cisplatin-etoposide x 11, rechallenge with EMA-CO x 20 and EMA-EP x 12) owing to a series of recurrences from March 2012 to March 2018. The patient became exhausted after undergoing chemotherapy for 6 years, making it difficult for her to undergo further cytotoxic treatments. Despite her stable disease status, a 2.5-cm vaginal metastatic lesion remained at the peri-urethral area (Fig. 1-D-④). IHC of the tumour showed 50% PD-L1 expression using the 22C3 antibody (Dako, Santa Clara, CA) (Fig. 1-A-③,④), and MSI status was determined to be high using multiplex PCR with five quasi-monomorphic mononucleotide repeat markers (Fig. 1-B). Treatment with pembrolizumab was initiated (200 mg fixed dose, every 3 weeks). The β-hCG level decreased steadily in the initial (57 IU/L) but did not normalise as treatment progressed. After the 11th cycle, the remaining tumour was discharged by itself through the urethra during urination (Fig. 1-D-④,⑤,⑥), and complete serologic remission (<5 IU/L) was finally achieved (Fig. 1-C). There was no histologic difference between the initial tissue and expulsed tissue. There were no additional adverse effects of treatment other than a grade II skin rash.

Table 1
Treatment response to pembrolizumab in chemoresistant GTN by literature.

Tumour type	Age	WHO score	Previous cycles of CTx	MSI status	PD-L1 expression (%)	No. of pembrolizumab treatment		Response	F/U after treatment (months)	Adverse events (grade)	Reference
						Cycles to serologic remission	Consolidation cycles				
CC	26	18	#8	N/A	Strong	#2	#4[a]	CR		Hepatotoxicity [3]	[4]
CC	42	17	#25	N/A	100	#4	#5	CR	>24	Arthralgia [1]	[1]
ETT/PSTT	52	8	#12	N/A	>90	[b]		PD		Pruritus [1]	
PSTT	48	20	#31	N/A	>90	#8	#5	CR	>15	Synovitis [1], rash [1]	
CC	37	6	#18	N/A	100	#2	#5	CR	>5	Neutropenia [2], synovitis [1]	
PSTT	39	15	#20	High	100	#1	#13	CR	>5	Hepatotoxicity [1]	Our study
ETT	49	14	#78	High	50	#11	#4 ongoing	PR	Ongoing	Skin rash [2]	

Abbreviation: GTN, gestational trophoblastic neoplasia; CC, choriocarcinoma; ETT, epithelioid trophoblastic tumour; PSTT, placental site trophoblastic tumour; CTx, chemotherapy; MSI, microsatellite instability; PD-L1, programmed cell death ligand 1; CR, complete remission; PD, persistent disease; PR, partial response; N/A, not applicable; WHO, World Health Organisation.

[a] 50% dose reduction d/t grade III hepatotoxicity.

[b] five cycles of pembrolizumab, although progression.

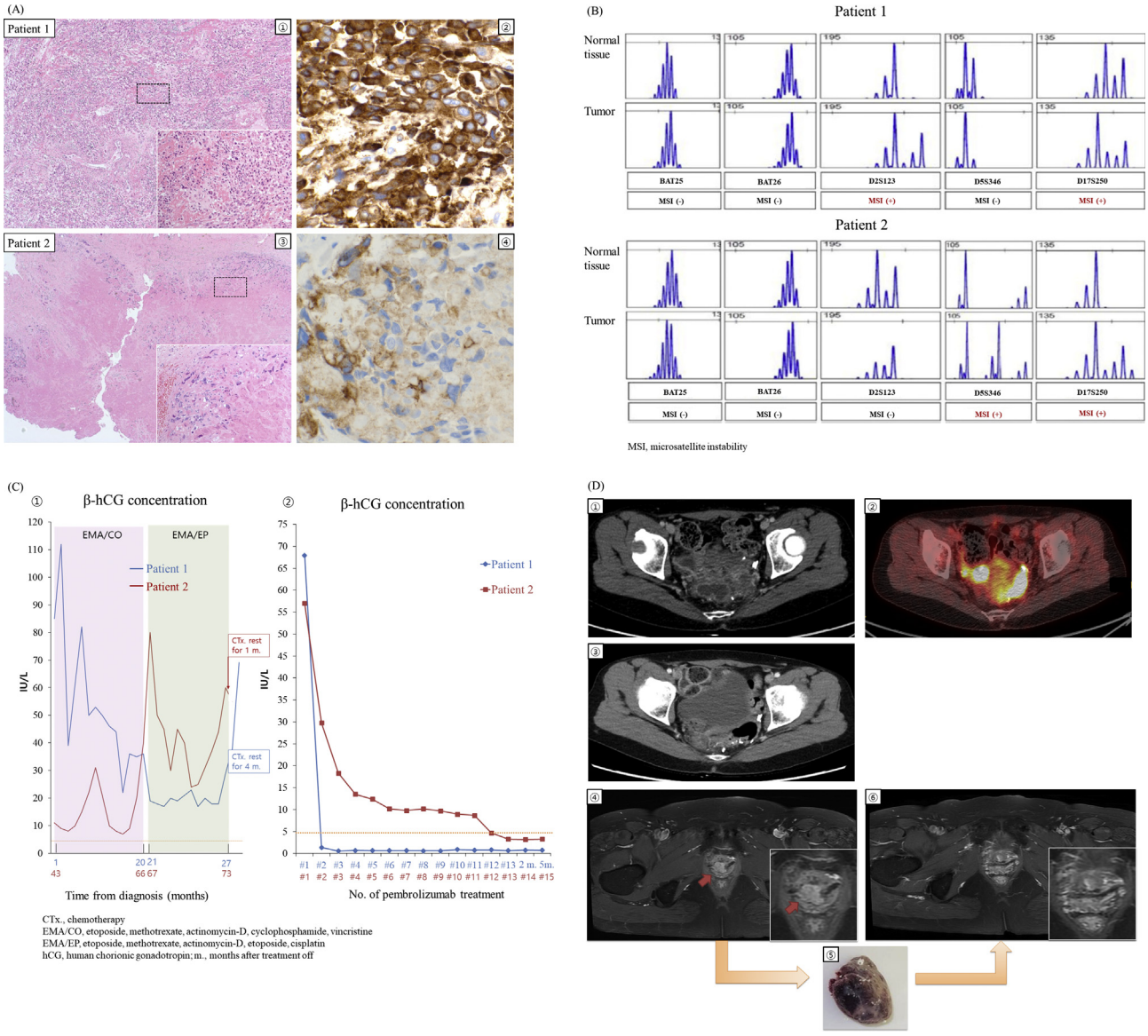

Fig. 1. **(A)** Haematoxylin and eosin section demonstrating PSTT (①, patient 1) and ETT (③, patient 2) (magnification, *100 and *200). ① shows neoplastic intermediate trophoblastic cells at the implantation site arranged as sheets of polyhedral, round or occasionally spindle-shaped cells that infiltrate the myometrium and extensively invading the vessel wall. Sheets of polygonal intermediate trophoblasts were observed in a background of fibrinous material. ③ shows nodular and well-circumscribed, focally infiltrative tumour cells at the periphery. Tumour cells are relatively uniform, mononucleate, and arranged in nests and cords. Tumour nests are intimately associated with an eosinophilic, fibrillar, hyaline-like material. Extensive geographic necrosis is present. Immunohistochemistry (②, 100% expression, patient 1; ④, 50% expression, patient 2) for PD-L1 showing diffuse membranous staining in tumour cells (magnification, *400). **(B)** Both patients' tumours revealed high MSI. **(C)** Serum β-hCG concentration measured throughout previous chemotherapies (①) and pembrolizumab treatment (②). Blue represents patient 1, and red does patient 2. **(D)** CT ① and PET ② imaging demonstrating multiple metastatic lesions in the pelvis before initiation of pembrolizumab and ③ after the 5th cycle, demonstrating CR status in patient 1. CT ④ imaging demonstrating 2.5-cm-sized mass at the peri-urethral region before the initiation of pembrolizumab and ⑥ after self-expulsion of the mass ⑤ at the 11th cycle, demonstrating radiologic near CR status in patient 2. PSTT, placental site trophoblastic tumour; ETT, epithelioid trophoblastic tumour; PD-L1, programmed cell death ligand 1; CT, computed tomography; PET, positron-emission tomography; CR, complete response; MSI, microsatellite instability; b-hCG, β-human chorionic gonadotropin.

Current disease status is near CR radiologically, and her treatment is ongoing.

Our patients initially presented with chemorefractory GTN but experienced dramatic improvement after pembrolizumab treatment. To the best of our knowledge, this is the first report on MSI status assessment and use of anti–PD-1 inhibitor for PSTT and ETT in Asia. Treatment outcomes with pembrolizumab for refractory GTN (including our study) showed a favourable response rate of 85.7% (6/7) and a

CR rate of 71.4% (5/7) (Table 1). Moreover, the European Society for Medical Oncology (ESMO) 2018 Congress announced that the CR rate was 50% (3/6) in a prospective phase II trial using avelumab, an anti–PD-L1 monoclonal antibody [5]. It may be a great model for immuno-oncology treatment by proving vastly superior to the response rate of immune checkpoint inhibitors in other malignancies. Efficacy and favourable toxicity profile of the PD/PD-L1 inhibitor could make its active and immediate application an appealing alternative to multi-agent chemotherapy. Although it has recently been added to the NCCN guideline based on the aforementioned literature, we recommend early use of PD-1/PD-L1 inhibitors in patients with chemoresistant GTN. We aim to conduct a multicentre clinical trial of anti–PD-1 therapy for many patients with GTN in Asia. In conclusion, PD-1–directed therapy with pembrolizumab presents an important novel treatment strategy for the management of chemo-resistant/refractory GTN that should strongly be considered and warrants further investigation.

Conflict of interest statement

The authors declare that they have no competing interests.

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