Original Article: Case Series

A case series on the efficacy and safety of a PD-1 inhibitor combined with antiangiogenic agents in the treatment of recurrent MSI-H endometrial cancer

Hualin Song[1,2,3#], Zhihua Du[4#], Huiting Xiao[1,2,3], Jing Tian[1,2,3], Ke Wang[1,2,3], Wenxin Liu[1,2,3]

[1]Department of Gynecological Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China; [2]Key Laboratory of Cancer Prevention and Therapy, Tianjin, China; [3]Tianjin's Clinical Research Center for Cancer, Tianjin, China; [4]Department of Oncology, Affiliated Hospital of Hebei University of Traditional Chinese Medicine, Hebei Provincial Hospital of Traditional Chinese Medicine, Shijiazhuang, China

Contributions: (I) Conception and design: W Liu; (II) Administrative support: K Wang; (III) Provision of study materials or patients: H Xiao; (IV) Collection and assembly of data: H Song, Z Du; (V) Data analysis and interpretation: J Tian; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Wenxin Liu, PhD. Department of Gynecological Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, West Huan-Hu Road, Hexi District, Tianjin 300060, China; Key Laboratory of Cancer Prevention and Therapy, Tianjin, China; Tianjin's Clinical Research Center for Cancer, Tianjin, China. Email: wenxin1973@163.com.

Background: Endometrial cancer (EC) is one of the most common gynecological malignancies in developed countries worldwide. The treatment of recurrent endometrial cancer is a very difficult problem in clinical work. Studies on patients with recurrent EC microsatellite instability-high (MSI-H) are very rare. The objective of this study is to initially evaluate the therapeutic effect of a PD-1 inhibitor combined with antiangiogenic agents in the treatment of recurrent MSI-H endometrial cancer.

Methods: Eight patients with recurrent MSI-H endometrial cancer were recruited from Tianjin Medical University Cancer Institute and Hospital from July 2019 to July 2021, and their median age was 55.3 (range, 46–62) years. All patients experienced recurrence after surgical treatment, and the median recurrence and metastasis time was 6.6 (range, 4–10) months. The pathological types were all endometrioid carcinomas. PD-1 inhibitors were selected from camrelizumab or pembrolizumab, and antiangiogenic targeted agents were selected from apatinib or anlotinib.

Results: The median follow-up time was 11.0 (range, 5–19) months. In the case series, all 8 cases could be evaluated for curative effect with complete response in 4 cases and partial response in 4 cases. The overall objective response rate was 100%.

Conclusions: PD-1 inhibitors combined with antiangiogenic agents may have good therapeutic effects on patients with recurrent MSI-H endometrial cancer and may become an important method for the treatment of recurrent endometrial cancer in the future.

Keywords: Endometrial cancer; PD-1; antiangiogenic agent; immunotherapy; case series

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Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries in Europe and the United States. In China, endometrial cancer ranks second in the incidence of gynecological malignancies, accounting for 3.88% of all new female cases (1,2). The proportion of endometrial cancer in the early stage is high, approximately 75%, and the prognosis is relatively good, with a 5-year survival rate ranging from 74–91% (1-3). However, patients with advanced or high-risk factors have a high recurrence rate of up to 50% (4-7). Once recurrence and metastasis occur, treatment becomes extremely difficult. At present, the treatment options for patients with recurrence and metastasis of EC are diverse. For a single recurrent lesion, surgical resection or radiotherapy can be selected, combined with systemic therapy. For patients with multiple or extensive recurrent lesions, systemic therapy based on chemotherapy is more suitable, and local radiotherapy is also optional. Despite adjuvant chemotherapy and other comprehensive treatments, the prognosis is still poor. The 5-year survival rate is less than 20% (7,8). High microsatellite instability-high (MSI-H) may lead to an increased risk of disease and recurrence of various malignancies, including EC and colorectal cancer (9), and approximately 30–40% of patients with endometrial cancer present with MSI-H (3,4). At present, some foreign clinical trials using PD-1 inhibitors in the treatment of MSI-H recurrent EC patients have found good efficacy (4,10-12). The application of immune drugs, especially PD-1 inhibitors, in EC is gradually being clinically recognized. However, studies on patients with recurrent EC MSI-H/mismatch repair deficiency (dMMR) are very rare. Even fewer studies have been conducted on PD-1 inhibitors combined with antiangiogenic agents in MSI-H/dMMR EC patients. The effect of combining antiangiogenic agents with PD-1 inhibitors in the treatment of patients with recurrent MSI-H/dMMR endometrial cancer is still unclear and needs further research. This article briefly analyses the efficacy of PD-1 inhibitors and antiangiogenic agents in 8 patients with MSI-H/dMMR relapsed EC. We present this article in accordance with the AME Case Series reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-275/rc).

Highlight box

Key findings

- PD-1 inhibitors combined with antiangiogenic agents have good therapeutic effects on patients with recurrent MSI-H endometrial cancer and may become an important method for the treatment of recurrent endometrial cancer in the future.

What is known and what is new?

- PD-1 inhibitors combined with antiangiogenic agents have good therapeutic effects on patients with recurrent MSI-H endometrial cancer.
- There are new therapeutic approaches for recurrent MSI-H endometrial cancer.

What is the implication, and what should change now?

- This paper suggests that PD-1 inhibitors combined with antiangiogenic drugs may be a good treatment for recurrent MSI-H endometrial cancer in the future, and clinicians should give more attention to the microsatellite status of recurrent endometrial cancer and use the above drugs for treatment.

Methods

Study design and participants

This study is a case series study conducted by Tianjin Medical University Cancer Institute and Hospital. From July 2019 to July 2021, 8 patients with recurrent MSI-H endometrial cancer were enrolled. The inclusion criteria were as follows: (I) the pathological type was endometrioid adenocarcinoma; (II) all patients underwent surgery, chemotherapy [paclitaxel (175 mg/m^2) + carboplatin (TC), area under the curve (AUC) =5] regimen for 4–6 courses and/or radiotherapy; (III) MSI-H was identified by high-throughput sequencing; and (IV) PD-1 inhibitor (camrelizumab or pembrolizumab) combined with antiangiogenic drugs agent (apatinib or anlotinib) was administered after recurrence. We collected the patients' age, pathological type, stage, grade, surgery, radiotherapy and chemotherapy, recurrence time and site, medications and prognosis after recurrence.

Follow-up evaluation was performed monthly for the first 6 months and every 3 months thereafter, during which ultrasound or computed tomography (CT) examinations were performed. Pathological results were accepted after independent pathologic review and confirmation by at least two pathologists. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Tianjin Medical University Cancer Institute and Hospital (No. bc2023001). Written informed consent was obtained from the patients for publication of this case series and

accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

The response evaluation criteria for patients with solid tumors [modified Response Evaluation Criteria in Solid Tumors (mRECIST)] jointly formulated by the National Cancer Institute of the United States, the National Cancer Institute of Canada and the European Organization for Cancer Research and Treatment were divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response (ORR) rate was considered the sum of CR and PR and was calculated by this method.

High-throughput sequencing and immunohistochemistry (IHC)

Postoperative specimens and blood samples were sent to testing companies for high-throughput testing, including MSI-H testing. The testing company is Geneseeq, based in Nanjing, China.

We then performed immunohistochemical tests on tissue obtained from surgical specimens. The markers detected were MLH1, MSH2, MSH6 and PMS2. The surgical tissue was fixed in 4% formalin buffer at 4 ℃ overnight, dehydrated, and conventionally embedded in paraffin. Then, the paraffin was cut into 5 μm sections. After dewaxing and hydration, 3% hydrogen peroxide was used to inactivate endogenous peroxidase. The primary antibodies against MLH1, MSH2, MSH6 and PMS2 were incubated overnight at 4 ℃, recognized by a biotinylated secondary antibody for 30 min at room temperature and visualized by a Vectastain ABC system and a peroxidase substrate DAB kit.

Results

Eight eligible patients, with a median age of 55.3 (range, 46–62) years, had various stages of endometrial cancer. After surgery (uterus + double appendage + pelvic lymph node dissection + para-aortic lymph node dissection/resection), the postoperative pathology was endometrioid adenocarcinoma, and International Federation of Gynecology and Obstetrics (FIGO) staging revealed 4 patients with stage Ia, 1 with stage Ib, 1 with stage IIIc1 and 2 with stage IIIc 2.

According to the postoperative pathological results, patients with stage Ib or above or stage Ia with high-risk factors were given adjuvant first-line therapy and/or radiotherapy, and a total of 6 patients in this study were given adjuvant therapy. The average recurrence and metastasis time of patients was 6.6 (range, 4–10) months, and the recurrence sites were the abdominal and pelvic cavities, supraclavicular lymph nodes and retroperitoneum. After recurrence, they were given second-line therapy. Among them, 6 patients received nab-paclitaxel/doxorubicin liposome + nedaplatin/oxaliplatin chemotherapy for 6–8 courses, and 3 patients received radiotherapy in the abdomen, pelvis, neck and shoulder areas. The treatment effect was not good, high-throughput gene sequencing showed MSI-H, and then combined treatment with a PD-1 inhibitor and antiangiogenic agents was given. The second-line treatment was directly administered with a combination of PD-1 inhibitors and antiangiogenic agents (*Table 1*).

All 8 patients in this study were finally determined to be MSI-H by high-throughput sequencing technology, and 6 of them were identified as dMMR by immunohistochemical analysis. The genetic testing results showed the following: tumor mutations, 92.4 (range, 60–141) Muts/Mb, and TMB, 50.6 (range, 43.7–81.6) Muts/Mb. Afterward, PD-1 inhibitor and antiangiogenic agent combination therapy was given.

The median follow-up time in this study was 17.0 (range, 11–25) months. The 8 patients in this group received PD-1 inhibitors combined with antiangiogenic targeted agent therapy for an average of 7.4 months (IQR, 5–13 months), and the average onset time was 2.1 (range, 1–4) months, including 4 cases of CR, 4 cases of PR, and 100% ORR (*Figure 1*). The specific pathological characteristics and curative effects of the patients are shown in *Table 1*.

Discussion

In recent years, the development of high-throughput sequencing technology has deepened our understanding of the pathogenesis and molecular genetic characteristics of endometrial cancer, and individualized and precise treatment based on molecular genetic characteristics has revolutionized the treatment of endometrial cancer. However, the molecular typing of endometrial cancer, its clinical value for prognosis evaluation and treatment selection, and the clinical value of molecular detection in patients with advanced endometrial cancer are still insufficiently understood. At present, the effect of combining antiangiogenic agents with PD-1 inhibitors in the treatment of patients with recurrent MSI-H/dMMR endometrial cancer is still unclear and needs further research and discussion. This study analyzed the preliminary efficacy of 8 patients with PD-1 inhibitors combined with antiangiogenic agents in the treatment of

Table 1 Pathological characteristics of 8 patients with recurrent MSI-H endometrial cancer and therapeutic effects of treatment with a PD-1 inhibitor combined with antiangiogenic targeted drugs

Cases	Age (years)	Stage	Grade	First-line chemotherapy	Radiotherapy	Follow-up (months)	Relapse (months)	Site of recurrence	Chemotherapy for recurrence	Radiotherapy for recurrence	Regimen	Medication time (months)	Onset time (months)	Efficacy
1	52	Ia	2	–	–	20	6	Pelvic cavity	Albumin-paclitaxel + nedaplatin	–	Camrelizumab + apatinib	9	2	PR
2	49	IIIc1	2	TC	Pelvis + vaginal	25	4	Supraclavicular lymph nodes	Doxorubicin liposome + nedaplatin	Neck and shoulders	Camrelizumab + anlotinib	13	4	CR
3	46	Ia	3	TC	Vaginal	18	6	Abdominal cavity	Albumin-paclitaxel + oxaliplatin	Abdominal pelvis	Pembrolizumab + anlotinib	6	2	PR
4	57	Ia	2	TC	–	16	10	Pelvic cavity	–	–	Camrelizumab + apatinib	6	1	CR
5	60	IIIc2	3	TC	Pelvis + abdominal aorta + vaginal	19	9	Retroperitoneal	Doxorubicin liposome + oxaliplatin	–	Camrelizumab + anlotinib	7	3	PR
6	56	Ia	2	–	–	11	7	Pelvic cavity	–	–	Camrelizumab + anlotinib	5	2	PR
7	60	IIIc2	3	TC	Pelvis+ abdominal aorta + vaginal	14	5	Abdominal cavity	Albumin-paclitaxel + nedaplatin	Abdominal pelvis	Pembrolizumab + anlotinib	7	1	CR
8	62	Ib	2	TC	Vaginal	13	6	Pelvic cavity	Doxorubicin liposome + nedaplatin	–	Camrelizumab + anlotinib	6	2	CR

MSI-H, microsatellite instability-high; TC, paclitaxel (175 mg/m^2) + carboplatin; PR, partial response; CR, complete response.

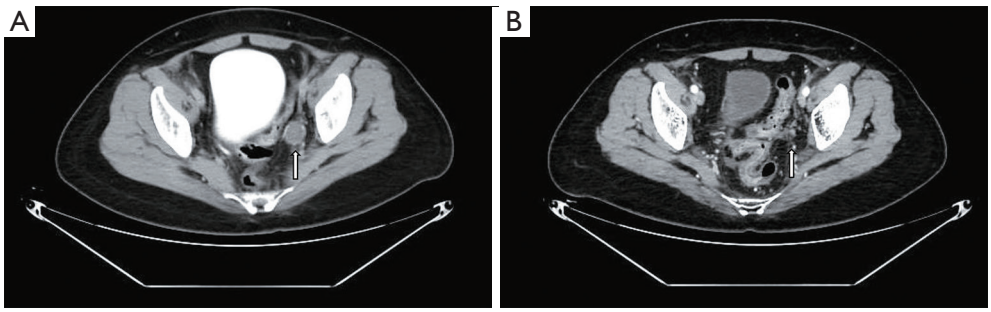

Figure 1 CT images before and after the therapeutic effect of a PD-1 inhibitor combined with antiangiogenic drugs in the treatment of recurrent MSI-H endometrial cancer. (A) Before treatment; (B) after treatment. Arrows indicate tumor lesions before (left) and after treatment (right). CT, computed tomography; MSI-H, microsatellite instability-high.

recurrent MSI-H/dMMR endometrial cancer in our center, which provided some experience and ideas for the further application of this treatment plan.

Microsatellites, also known as short tandem repeats, are repetitive DNA sequences distributed in coding and noncoding regions of the genome (13). The existence of microsatellite instability is phenotypic evidence that mismatch repair genes do not function properly (14). Four genes play an important role in the process of DNA mismatch repair: MLH1, MSH2, MSH6 and PMS2. Germline and/or somatic mutations or epigenetic silencing may result in inactivation of any of these genes, resulting in dMMR. Sporadic MSI is caused by methylation of the promoter region of the repair gene MLH1, whereas Lynch syndrome is caused by an autosomal dominant germline mutation of MLH1, MSH2, MSH6 or PMS2 (14). Immunohistochemistry was used in most studies to detect MSH2, MSH6, MLH1, and PMS2, and dMMR was diagnosed when one of them was negative, while PCR or high-throughput sequencing techniques were usually used to detect MSI status. MSI-H and dMMR are both similar and different. In many studies, the two are common but not identical. Notably, many dMMR patients show MSI-H, while not all MSI-H patients show dMMR. The diagnostic results of MSI-H in this article were all derived from high-throughput sequencing, and 6 of the 8 MSI-H patients had dMMR.

In recent years, some clinical trials have found that immunotherapy represented by PD-1 inhibitors has shown good efficacy in EC with recurrent MSI-H (4,10-12). KEYNOTE-158 is a phase II study in patients with a variety of advanced solid tumors. In 2019, O'Malley analyzed 49 patients with MSI-H/dMMR endometrial cancer and found that the overall ORR reached 57% (15). In 2019, Konstantinopoulos found that the PD-1 inhibitor avelumab showed good effects in patients with recurrent or persistently progressive endometrial cancer in dMMR (16). In 2021, Oaknin reported on a clinical trial of the PD-1 inhibitor dostarlimab as a monotherapy in patients with relapsed or advanced dMMR/MSI-H and found that dostarlimab successfully shrunk 42% of these patients' tumors (10). In 2021, Bellone reported the results of a phase II clinical trial of pembrolizumab in patients with relapsed MSI-H and found that the overall ORR was 58% (36.6–77.9%) (17). The latest NCCN 2021 guidelines recommended pembrolizumab as a single agent for advanced endometrial cancer with MSI-H/dMMR (18).

At the same time, the latest 2021 NCCN recommended pembrolizumab combined with lenvatinib for non-MSI-H/dMMR recurrent and metastatic endometrial cancer (18). However, the therapeutic effect of PD-1 inhibitors combined with antiangiogenic agents in the treatment of MSI-H/dMMR patients with recurrent EC remains to be further explored, and relevant studies are rare at home and abroad. In 2020, Makker reported on the KEYNOTE-146 study showing the effect of pembrolizumab combined with lenvatinib in the treatment of patients with advanced endometrial cancer (n=108) and found that the overall ORR was 38.0% (28.8–47.8%), while the ORR was 63.6% (30.8–89.1%) in the MSI-H subgroup (n=11) (19). The 2021 NCCN recommended the use of pembrolizumab combined with lenvatinib for non-MSI-H/dMMR recurrent and metastatic endometrial cancer based on the KEYNOTE-146 study results but did not recommend this regimen for MSI-H/dMMR. Although good data were obtained in the MSI-H subgroup, the conclusion has yet to be confirmed due to the small number of patients. In 2022, Makker continued to report the results of the KEYNOTE-775 study. Among patients with dMMR, the

ORR of patients with advanced endometrial cancer treated with pembrolizumab combined with lenvatinib was 40% (28–53%), while the ORR of the chemotherapy group was only 12% (5–23%). Nevertheless, the author only affirmed the efficacy of the MMR normal group and the general population when drawing conclusions but did not give a positive conclusion to the dMMR patient group because the number of patients included was still insufficient (20). With the deepening of the understanding of endometrial cancer, clinicians will consider and choose drugs according to different molecular subtypes of endometrial cancer, and MSI-H/dMMR is a very important molecular state. There are several ongoing clinical studies which monoclonal antibodies have been evaluated for the treatment of tumors expressing high levels of immune checkpoint-associated proteins (21-24). The results also indicate that advanced or metastatic stages could benefit from targeted adjuvant therapies based on molecular alterations, particularly considering advanced MSI-H/dMMR (21,22). According to the pathological results of the 8 patients reported in this article, they all relapsed within 1 year after receiving first-line treatment or clinical observation, and the average recurrence time was 6.6 (range, 4–10) months. In our case series, PD-1 inhibitors combined with antiangiogenic agents achieved good therapeutic effects, and the overall ORR was 100%, which may be useful for future treatment of MSI-H recurrent endometrial cancer. The clinical efficacy of molecular precision therapy has the potential for exploration. However, the sample size of this study is small, and more clinical randomized controlled trial data or multicenter retrospective study data are needed to verify the conclusions of this study in the future.

Conclusions

In summary, the treatment of recurrent endometrial cancer is difficult. Clinically, molecular detection of MSI status can be performed for patients with recurrent endometrial cancer, and PD-1 inhibitors can be used for patients with recurrent MSI-H endometrial cancer. PD-1 inhibitors combined with antiangiogenic agents may have good therapeutic effects and may become an important means of molecular precision therapy for recurrent endometrial cancer in the future.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-275/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-275/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-275/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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (No. bc2023001). Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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