Original Article

Safety and efficacy of sintilimab combination therapy for the treatment of 48 patients with advanced malignant tumors

Nana Huang, Chenchen Zhao, Xueyang Hu, Congjun Zhang, Fuxing Xiong, Wei Huang, Liangshan Da, Yuanyuan Shen, Hongyang Wu

Department of Medical Oncology, First Affiliated Hospital of Anhui Medical University, Hefei, China

Contributions: (I) Conception and design: H Wu, N Huang; (II) Administrative support: H Wu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: N Huang; (V) Data analysis and interpretation: N Huang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hongyang Wu, MD, PhD. Department of Medical Oncology, First Affiliated Hospital of Anhui Medical University, Hefei 230031, China. Email: wuhoya1970@163.com.

Background: Sintilimab is a recombinant fully human anti-programmed death 1 (PD-1) monoclonal antibody that blocks the interaction of PD-1 with its ligand. We evaluated the safety and efficacy of sintilimab combined with chemotherapy and targeted therapy in the treatment of advanced malignant tumors.

Methods: We performed a retrospective analysis of the clinical data of patients with advanced malignant tumors treated with sintilimab combined with chemotherapy and targeted therapy admitted to the Third Ward of the Department of Medical Oncology, First Affiliated Hospital of Anhui Medical University, China, from July 2019 to February 2021. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and related adverse reactions were analyzed.

Results: A total of 48 patients with advanced malignant tumors treated with sintilimab combined with chemotherapy and targeted therapy. All 48 patients completed 2 courses of treatment, and the ORR and DCR were 20.83% and 81.25%. The median PFS for all patients in this study was 7 months, and the median OS was not yet reached. The median PFS for the first-line and second-line patients was 10 months, and the median OS was not yet reached. The median PFS for third-line and beyond patients was 7 months, and the median OS was 10 months. The differences in PFS and OS were both statistically significant. Adverse events occurred in 24 patients, of which 18 patients had grade I-II adverse events and 6 patients had grade III-IV adverse events.

Conclusions: Sintilimab is an inexpensive PD-1 drug produced in China. Sintilimab combination therapy showed good safety in the treatment of advanced malignant tumors, with increases in the treatment efficacy and DCR for advanced tumors. Because of few adverse reactions and proven efficacy, sintilimab combination therapy can be used as an option for the treatment of advanced malignant tumors.

Keywords: Sintilimab; advanced malignant tumors; objective response rate (ORR); disease control rate (DCR); adverse reactions

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Introduction

In recent years, the incidence of malignant tumors worldwide has increased year to year, seriously affecting human health. The treatment of tumors has also progressed from approaches involving surgery, radiotherapy, and chemotherapy to precision targeted therapy, entering a new era of immunotherapy. The combination of classical tumor treatment methods and immune checkpoint inhibitors (ICIs) effectively improves the quality of life of tumor patients and prolongs the survival time of patients with advanced

tumors (1,2). Immune checkpoint molecules mainly include programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) (3,4). PD-1 is an important immunosuppressive molecule and a member of the CD28 superfamily (5). PD-1/PD-L1 inhibitors can block the binding of PD-1 and PD-L1, block negative regulatory signals, restore the activity of T cells, and enhance antitumor immune responses, thereby achieving an antitumor effect (6,7). PD-1 and PD-L1 inhibitors have shown significant efficacy in the treatment of a variety of advanced malignant tumors. Breakthroughs in the treatment of non-small cell lung cancer (NSCLC), esophageal cancer and microsatellite instable tumors have been achieved, as represented by PD-1 monoclonal antibodies and PD-L1 monoclonal antibodies (8-10). As such, they have been approved as therapeutic options for a variety of malignant tumors. In recent years, ICIs have placed a spotlight on immunotherapy in tumor treatment. The gradual introduction of inexpensive PD-1 monoclonal antibodies made in China can benefit more Chinese patients with advanced cancer. Sintilimab is a PD-1 antibody made in China, and studies have shown that sintilimab has higher levels of PD-1 occupancy than nivolumab and pembrolizumab in peripheral blood mononuclear cells (PBMCs) and in mice injected with PBMCs. In patients, after a single intravenous infusion of sintilimab, a sustained occupancy of ≥95% of PD-1 for 4 weeks was observed (11). In a variety of studies, this drug has shown good antitumor effects on various types of cancer.

Sintilimab combination therapy has been clinically tested in a variety of tumor treatments. In a multicenter, single-arm, phase II trial (ORIENT-1) that enrolled 96 adults with relapsed or refractory classical Hodgkin's lymphoma after 2 or more lines of chemotherapy, the objective response rate (ORR) was 80.4%, and the disease control rate (DCR) was 97.8%. Sintilimab has been approved for the treatment of relapsed or refractory classical Hodgkin's lymphoma because sintilimab is associated with a high remission rate and low toxicity (12,13). Results from ORIENT-11 and ChiCTR-OIC-17013726 suggest that sintilimab has good safety and tolerability and has satisfactory efficacy in NSCLC (14,15). Results from KEYNOTE-590 suggest that sintilimab also has good antitumor effects in esophageal cancer (16). Sintilimab has also been shown to be effective in the treatment of other tumors. The results of a clinical study regarding the efficacy of sintilimab in the treatment of advanced hepatocellular carcinoma were encouraging (17). In another retrospective single-center study involving 10 patients with advanced renal cell carcinoma, the ORR of sintilimab combined with axitinib was 40.00%, and the DCR was 90.00% (18). The above results suggest that sintilimab may be a new therapeutic option.

In China, many patients with advanced malignancies typically have poor performance status and often do not respond to first- and second-line treatments. The clinical benefits of immunotherapy, chemotherapy, or targeted therapy alone are not obvious in these patients. Therefore, immune-based combination therapies have been developed to further increase the clinical response rates of patients with advanced malignancies. Many clinical studies have demonstrated the high efficacy and low toxicity of sintilimab; in addition, the price of sintilimab is more affordable and acceptable for Chinese patients. This study focuses on the clinical treatment of advanced tumor patients actually treated in Anhui, China. It is a real-world study. This study retrospectively analyzed the efficacy and safety of sintilimab combined with chemotherapy and targeted therapy in patients with advanced malignant tumors. The treatment results will better reflect the intuitive and real clinical effect of sintilimab combined with chemotherapy and targeted therapy in clinical treatment, it can provide a guidance and reference in the treatment of patients with advanced tumor in the future. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-54/rc).

Methods

General information

The clinical data of patients with advanced malignant tumors who received sintilimab combined with chemotherapy and targeted drug treatment in the third ward of the Department of Oncology, First Affiliated Hospital of Anhui Medical University, China, from July 2019 to February 2021 were collected. Follow-up occurred until April 2021. As a retrospective study based on real-world data, our current study had certain limitations in the timeliness of the data and the number of cases, and thus we did not carry out analysis based on specific tumor subgroups. With larger sample size in the future, we will further explore whether the efficiency of sintilimab is higher in specific tumors than in other tumor types. All patients had a clear pathological diagnosis, with imaging indicating

advanced tumors and Eastern Cooperative Oncology Group (ECOG) scores ranging from 0 to 2 points. Patients with autoimmune system diseases and liver, lung or renal failure were excluded. The patients were expected to survive for more than half a year and signed informed consent forms for treatment. The drug withdrawal indications were treatment ineffectiveness, disease progression, intolerable toxicity, death, and abandonment of treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of First Affiliated Hospital of Anhui Medical University, Hefei, China (No. PJ2022-01-50) and individual consent for this retrospective analysis was waived.

Treatment regimens

All patients with advanced malignant tumors received sintilimab combination therapy. Patients received 200 mg (Recommended dose in drug instructions) sintilimab intravenously over a period of 30–60 min, once every 3 weeks, until disease progression, death, unacceptable toxicity, or withdrawal of consent, for a maximum of 24 months. Chemotherapy and targeted drugs were administered in accordance with standard treatment regimens.

Observation indicators

Before each treatment with sintilimab, the patients underwent routine blood tests, biochemical tests, thyroid function tests, myocardial enzyme analysis, and electrocardiography. Imaging examinations were performed every 2 treatment courses to evaluate efficacy, and adverse reactions during treatment were recorded in detail.

Evaluation of efficacy and adverse reactions

In accordance with RECIST 1.1, efficacy was evaluated and classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). ORR = (CR + PR)/total number of cases × 100%, and DCR = (CR + PR + SD)/total number of cases × 100%. Adverse reactions were evaluated in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Statistical analysis

Disease control was calculated as the proportion of patients with a best overall response of complete remission, partial remission, or stable disease. Time to response was defined as the time from the first treatment administration to the first incidence of treatment response (either complete remission or partial remission). Progression-free survival was defined as the time from first treatment administration to disease progression or death from any cause, whichever came first.

Kaplan-Meier survival curves were plotted using GraphPad Prism 8.3 (GraphPad Software Inc), with involvement of proportional hazard model and the Log rank test. $P<0.05$ was considered statistically significant.

Results

Clinical characteristics

From July 2019 to February 2021, a total of 48 patients (35 males and 13 females) were included in this retrospective analysis. The patients were 28–81 years old, with a median age of 59 years. Among the tumors, there were 3 cases of head and neck squamous cell carcinoma, 11 cases of esophageal cancer, 12 cases of gastric cancer, 2 cases of intestinal cancer, 2 cases of liver cancer, 1 case of gallbladder cancer, 2 cases of malignant melanoma, 2 cases of urothelial cancer, 7 cases of lung cancer, 2 cases of malignant lymphoma, 1 case of ovarian cancer, 1 case of soft tissue sarcoma, and 2 cases of breast cancer. The baseline characteristics of the patients are summarized in *Table 1*.

Treatment regimens

In this study, a total of 48 patients received sintilimab combined with chemotherapy. The chemotherapy regimen was selected based on the tumor type. The main chemotherapeutic drugs involved included gemcitabine, oxaliplatin, capecitabine, irinotecan, nab-paclitaxel, tegafur, and nedaplatin. Two patients received targeted drugs combined with anlotinib, 1 patient received a targeted drug combined with apatinib mesylate, and 1 patient received a targeted drug combined with sorafenib.

Efficacy assessment

All patients were treated with sintilimab for 2 courses or more. The ORR and DCR increased as the number of courses of sintilimab combined with chemotherapy increased. The ORR and DCR for the 2 courses of

Table 1 Clinical characteristics of patients with advanced tumors

Clinical characteristics of the patients	Number of patients (%)
Sex	
Male	35 (72.92)
Female	13 (27.08)
ECOG score	
0–1	40 (83.33)
2–3	8 (16.67)
Age	
≥60 years old	24 (50.00)
<60 years old	24 (50.00)
Tumor type	
Soft tissue sarcoma	1 (2.08)
Intestinal cancer	2 (4.17)
Esophageal cancer	11 (22.92)
Malignant lymphoma	2 (4.17)
Gastric cancer	12 (25.00)
Breast cancer	2 (4.17)
Liver cancer	2 (4.17)
Urothelial carcinoma	2 (4.17)
Ovarian cancer	1 (2.08)
Lung cancer	7 (14.58)
Malignant melanoma	2 (4.17)
Head and neck squamous cell carcinoma	3 (6.25)
Gallbladder cancer	1 (2.08)
Treatment regimen	
Sintilimab combined with chemotherapy	44 (91.67)
Sintilimab combined with apatinib	1 (2.08)
Sintilimab combined with anlotinib	2 (4.17)
Sintilimab combined with sorafenib	1 (2.08)
Treatment line	
First and second line	35 (72.92)
Third line and beyond	13 (27.08)
Treatment course	
2 courses or more	48 (100.00)
4 courses or more	27 (56.25)
6 courses or more	11 (22.92)
8 courses or more	7 (14.58)

treatment were 20.83% and 81.25%, respectively. Twenty-seven patients completed 4 or more courses; for these patients, the ORR and DCR were 44.44% and 81.48%, respectively. Eleven patients completed 6 or more courses; for these patients, the ORR and DCR were 54.55% and 81.82%, respectively. Seven patients completed 8 or more courses; for these patients, the ORR and DCR were 71.42% and 85.71%, respectively (*Table 2*). One patient with advanced nasopharyngeal carcinoma, a 53-year-old male, had pulmonary metastases with rapid progression after 2 courses of second-line treatment. The lesions in the lungs basically disappeared, and the efficacy was significant after 2 courses of third-line treatment with sintilimab and gemcitabine combined with cisplatin chemotherapy. The imaging changes are shown in *Figure 1*.

Progression-free survival (PFS)

By the end of the follow-up period, disease progression or death had been reported for 24 patients. Four patients withdrew from the follow-up early, and their data were censored. The overall median PFS was 7 months (*Figure 2A*). The median PFS for the 35 patients who received first-line or second-line treatment was 10 months, and the median PFS for the patients who received third-line treatment and beyond was 7 months, with a significant difference between the 2 groups (P<0.05). The efficacy for first-line and second-line patients was better than that for third-line and beyond patients (*Figure 2B*).

Overall survival (OS)

By the end of the follow-up period, 9 patients had died, and 35 patients were alive; 4 patients withdrew early from follow-up, and their data were censored. The overall median OS had not yet been reached (*Figure 3A*). Among the 35 patients who received first-line or second-line treatment, the median OS had not yet been reached. For the 13 patients who received third-line treatment and beyond, and the median OS was 10 months. The difference between the 2 groups was statistically significant (P<0.05) (*Figure 3B*).

Adverse reactions

In this study, 24 patients had adverse reactions, including 18 cases of grade 1–2 reactions and 6 cases of grade 3 and above reactions. In the other 24 patients, there were no adverse reactions. The incidence of all grades of immune-

Table 2 Evaluation of the efficacy of different treatment courses in patients with advanced tumors

Treatment course	Total number of patients	CR	PR	SD	PD	ORR	DCR
2 courses	48	0	10	29	9	20.83%	81.25%
4 courses	27	0	12	10	5	44.44%	81.48%
6 courses	11	0	6	3	2	54.55%	81.82%
8 courses	7	0	5	1	1	71.42%	85.71%

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; PR, partial response.

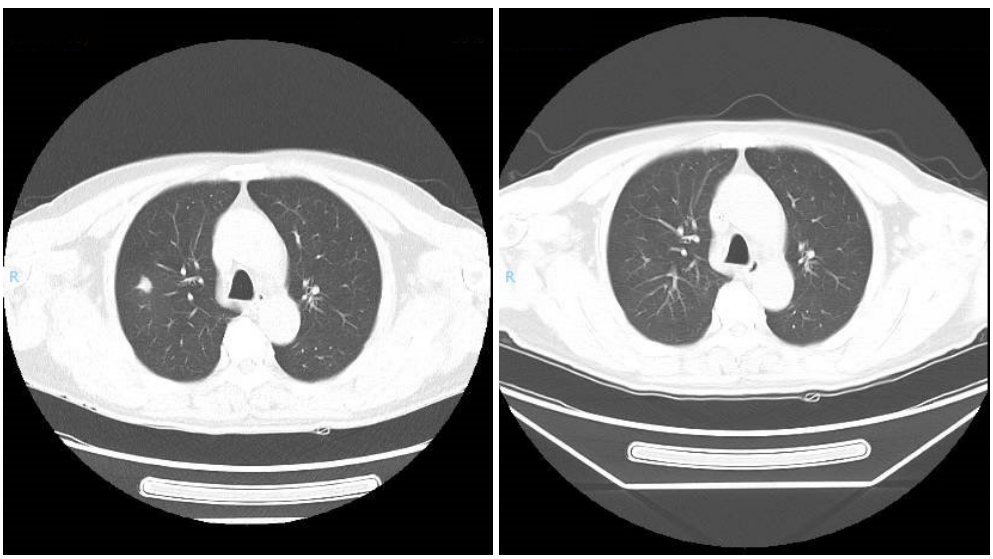

Figure 1 Nasopharyngeal carcinoma patient treated with sintilimab combination therapy; pulmonary lesions basically disappeared after 2 courses of treatment.

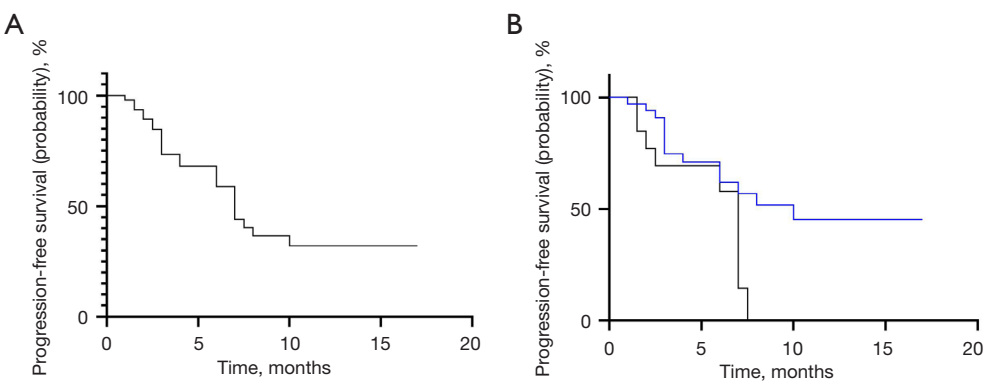

Figure 2 PFS of sintilimab in the treatment of advanced malignant tumors. (A) PFS of patients with advanced tumors who received sintilimab combination therapy. (B) The median PFS of first-line and second-line patients (blue line) was better than that of third-line and beyond patients (black line). PFS, progression-free survival.

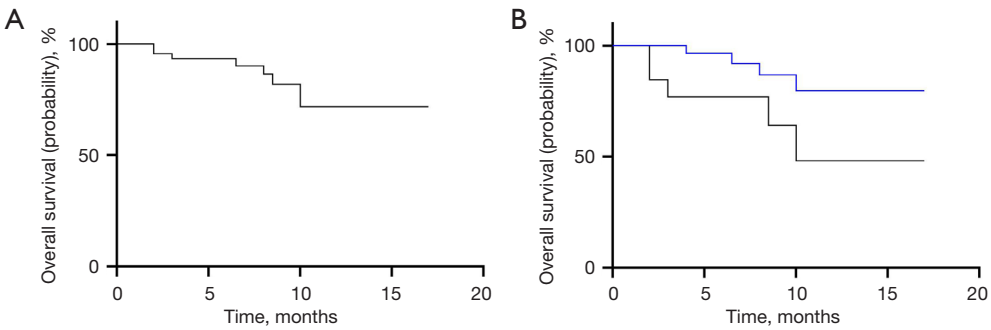

Figure 3 OS of sintilimab in the treatment of advanced malignant tumors. (A) OS of patients with advanced tumors who received sintilimab combination therapy; (B) The median OS of first-line and second-line patients (blue line) was better than that of third-line and beyond patients (black line). OS, overall survival.

Table 3 Adverse reactions related to immune combination therapy

Adverse reactions	Patient number, No. (%)		
	Grade 1–2	Grade 3 and above	All levels
Patients with adverse reactions	18 (37.50)	6 (12.50)	24 (50.00)
Skin reaction	2 (4.17)	–	2 (4.17)
Gastrointestinal reactions	7 (14.58)	2 (4.17)	9 (18.75)
Hypothyroidism	2 (4.17)	–	2 (4.17)
Liver damage	3 (6.25)	1 (2.08)	4 (8.33)
Immune-associated pneumonia	1 (2.08)	–	1 (2.08)
Immune-associated myocarditis	1 (2.08)	–	1 (2.08)
Bone marrow suppression after chemotherapy	5 (10.42)	2 (4.17)	7 (14.58)
Hypoproteinemia	7 (14.58)	2 (4.17)	9 (18.75)
Intestinal obstruction	1 (2.08)	–	1 (2.08)

related toxicity was 50.00%, the incidence of grade 1–2 toxic reactions was 37.50%, and the incidence of grade 3 and above toxic reactions was 12.50%. The most common adverse reactions were mainly grade 1 to 2, for example, gastrointestinal reactions, bone marrow suppression after chemotherapy, rash with itching, immune-related thyroid dysfunction, abnormal liver function, immune-related pneumonia, and immune-related myocarditis. Immunotherapy was permanently discontinued for 1 patient due to severe liver damage, and treatment was suspended for 1 patient due to immune-related myocarditis (*Table 3*).

Discussion

In this study, patients with a variety of advanced malignant tumors were enrolled. The median PFS after sintilimab combination treatment was 7 months. The median PFS for patients who received first-line and second-line regimens was 10 months, and the median OS had not yet been reached; these values were significantly better than those for patients who received third-line regimens and beyond and patients with high ECOG scores. Twelve patients were still using sintilimab at the end of the follow-up period.

Chemotherapy is a treatment that uses chemical drugs

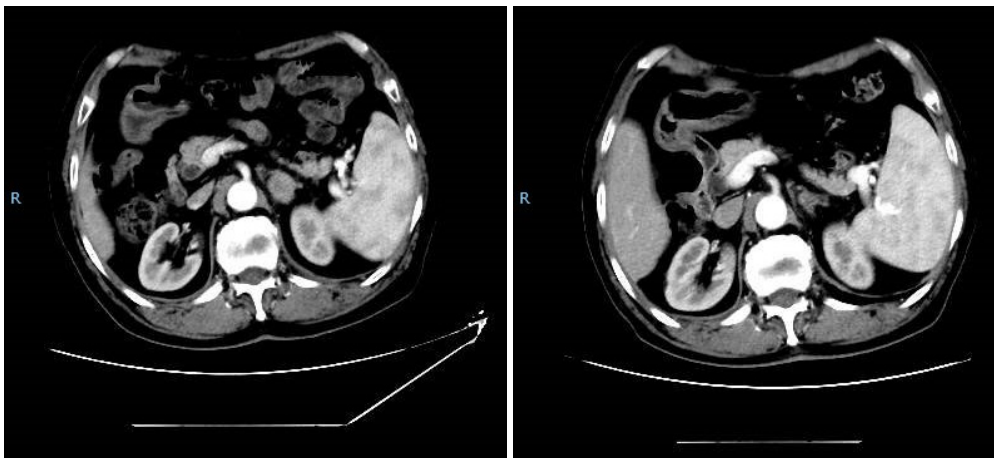

Figure 4 Lung squamous cell carcinoma (left) treated with 2 courses of second-line sintilimab combination therapy (right); the left adrenal lesion decreased significantly.

to prevent the proliferation, infiltration, and metastasis of cancer cells and to ultimately kill cancer cells. These drugs not only act on cancer cells but also affect normal cells in the body; furthermore, drug resistance can occur, limiting efficacy. Chemotherapy can induce the death of immunogenic tumor cells; therefore, immunotherapy may play a complementary role to chemotherapy. Results from KEYNOTE-590 (16) confirmed that the efficacy of immunotherapy combined with chemotherapy was superior to that of chemotherapy alone in advanced esophageal cancer. The KEYNOTE-189 (19), KEYNOTE-407 (20), and IMpower131 (21) clinical trials confirmed that in advanced NSCLC, the efficacy of immunotherapy combined with chemotherapy was superior to that of chemotherapy alone. In this study, the median PFS was 7 months, and the DCR was greater than 80%, results similar to the efficacy achieved by immunotherapy combined with chemotherapy in the abovementioned studies.

In the KEYNOTE-189 clinical trial (19), the PFS for epidermal growth factor receptor (EGFR) mutation-negative or ALK-negative advanced NSCLC patients who received first-line pembrolizumab combined with pemetrexed and platinum was 8.8 months, a result similar to those reported for the ORIENT-11 trial. Data from the phase 3 CheckMate-649 trial (22) showed that the first-line combination therapy of nivolumab and chemotherapy showed a survival benefit in patients with advanced gastric cancer, in contrast to the chemotherapy alone. ORIENT-16 (23) demonstrated sintilimab in combination with chemotherapy significantly prolonged OS (18.4 months) in the first-line treatment of advanced gastric cancer, superior to that of nivolumab. In addition to its low price, sintilimab also had significantly lower toxicities than pembrolizumab and nivolumab. These results indicate that sintilimab may be an equivalent substitute for pembrolizumab or nivolumab in China for first-line PD-(L)1 combined with chemotherapy.

Many patients in this study showed significant remission after 2 courses of treatment. A 68-year-old male patient had right lung squamous cell carcinoma recurrence 8 months after surgery. The first-line treatment was sintilimab (200 mg) combined with nab-paclitaxel (400 mg). After 2 courses of treatment, an evaluation indicated a significant reduction in the metastases in the left adrenal gland and right kidney, a decrease in carcinoembryonic antigen (CEA) from 15.64 to 2.65 ng/mL, PR, and a significant improvement in the patient's condition. The imaging changes are shown in *Figure 4*. We believe that sintilimab combination therapy has a significant effect in clinical practice.

Although sintilimab has shown effectiveness in the treatment of advanced malignant tumors, the potential side effects are still worthy of attention. In this study, the incidence of adverse events was 50.0% (24/48), and the incidence of grade 3 and above treatment-related adverse events (TRAEs) was 12.50% (6/48). There were no deaths caused by drug-related side effects. Among the adverse events, there were 4 cases of liver damage, with 3 cases that were grade 2 or less and 1 case that was grade 3; however, none of these 4 cases involved underlying liver disease. The 3 patients with grade 2 or less liver damage

improved with symptomatic management and continued to receive sintilimab combination therapy. The patient with grade 3 liver damage was treated with hormones in combination with hepatoprotective therapy and gradually improved, without continuing treatment with sintilimab. In addition, among the adverse events, 1 case of myocarditis and 1 case of pneumonia occurred; although both may have been immune-related adverse events caused by sintilimab, their severity did not exceed grade 2. The grade 3 adverse events were mainly gastrointestinal reactions, bone marrow suppression, and hypoproteinemia, all of which were considered to be chemotherapy-related side effects. The incidence and severity of adverse reactions to sintilimab combined with chemotherapy were basically consistent with those of chemotherapy drugs with known side effects. The addition of immunotherapy did increase the number of adverse events, and most adverse events were grade 1 to 2. These results are consistent with those reported by Vincent K. Lam (24) in a study of sintilimab combined with chemotherapy in patients with lung cancer and are similar to those for NCT02937116 (25), which investigated sintilimab combined with chemotherapy in patients with gastric cancer. Compared with nivolumab or pembrolizumab, sintilimab is less toxic and has been proven to be safe (26-29).

This was a retrospective study with a small sample size. The results need to be further confirmed by large-sample prospective clinical trials. Due to the diversity of combination treatment regimens, a comparative analysis between different regimens was not performed. In addition, the follow-up time was limited, and OS data were still being gathered. Initially, we planned to assess PD-(L)1 expression and efficacy. However, referring to relevant immunotherapeutic drugs in China, such as camrelizumab and toripalimab, we found that although PD-L1 expression was low or not detected, combined treatment still achieved good efficacy. A larger sample size would allow the detailed detection of immunotherapy-related markers, which may be beneficial for efficacy analyses. Our study data are based on observations of the clinical efficacy of sintilimab combination treatment in patients with advanced malignant tumors. The results of this study have certain guiding value for the future application of immunological drugs for the treatment of advanced malignant tumors.

Conclusions

Sintilimab combination therapy increases the treatment efficacy for patients with a variety of advanced tumors, and there is no significant increase in adverse events. The efficacy of sintilimab combination therapy for the treatment of more tumor types should be explored. In the future, sintilimab may be an important option for the clinical treatment of these advanced malignant tumors.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-54/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-54/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-54/coif). HW received funding from the project Phase II clinical Study of The Efficacy and Safety of A PD-1 Monoclonal Antibody Combined with Nab-Paclitaxel in The Second-Line Treatment of Patients with Advanced Esophageal and Gastric Junction Squamous Cell Carcinoma (No. 320.6750.2020-10-27, to HW). The other 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). The study was approved by institutional ethics board of First Affiliated Hospital of Anhui Medical University, Hefei, China (No. PJ2022-01-50) and individual consent for this retrospective analysis was waived.

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