A Real-World Study of The Efficacy and Safety of Sintilimab in The Treatment of Recurrent or Refractory Lymphoma

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Abstract

Background: Sintilimab (Innovent Biologics, China, Suzhou, China) has been listed in China for only a year and a half. So far, there have been no reports about it in real research. The purpose of this study was to evaluate the efficacy and safety of the real-world use of Sintilimab in the treatment of recurrent or refractory lymphoma and to explore the factors that influence the efficacy and safety of Sintilimab.

Methods: Based on real world data, a retrospective analysis of 25 patients with relapsed or refractory lymphoma treated with Sintilimab was performed.

Results: Efficacy was evaluable in 19 of 25 patients, objective response rate (ORR), disease control rate (DCR) and clinical response rate (CBR) were 63.2%, 84.2% and 73.7%, respectively. Among the different pathological types, Hodgkin's lymphoma ORR 77.8%, CBR 100%, diffuse large B-cell lymphoma ORR 25%, CBR 0%, peripheral T/NK cell lymphoma ORR 66.7%, CBR 83.3%. The number of previous chemotherapy courses was correlated with the short-term efficacy of the patients ($P=0.029$). In the safety analysis, 76% of treatment-related adverse events occurred, 80% of which were grade 1 and 2, with the major adverse events being hypothyroidism and anemia. Hypothyroidism is related to sex.

Conclusions: Sintilimab is effective in recurrent or refractory lymphoma and the adverse reactions are controllable. The fewer the lines of previous chemotherapies, the better the short-term efficacy of Sintilimab. The use of Sintilimab in female patients should be paid more attention to thyroid function.

1. Background

There are two major types of malignant lymphoma (ML): Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) [1]. Although effective remission and long-term control can be achieved in patients with malignant lymphoma after standard system treatment, there are still some patients who do not respond to initial treatment, and some patients relapse after complete remission. In addition to chemotherapy, radiotherapy, targeted therapy or stem cell transplantation [2, 3], the efficacy of PD-1 / PD-L1 inhibitors in the treatment of lymphoma has been gradually confirmed clinically in recent years with the understanding of PD-1 and PD-L1 pathways[4].

Sintilimab has been co-developed by Innovent Biologics and Eli Lilly and Company, was approved by the China Medical Products Administration in December 2018 for the treatment of recurrent or refractory classical Hodgkin lymphoma (cHL). It is a fully human IgG4 monoclonal antibody (mAb) produced using yeast display technology, which can block the binding of PD-1 to PD-L1 or PD-L2 and restore the anti-tumor activity of T cells. A multicenter, one-arm, phase II trial was conducted for the safety and activity of Sintilimab in patients with recurrent or refractory typical Hodgkin's lymphoma (ORIENT-1), and the results demonstrated good Sintilimab activity, safety, and tolerability[5]. Sintilimab has been on the market for only one and a half years, so far it has not been reported in the real world. In this study, a retrospective analysis was conducted on 25 patients with refractory recurrence in actual work, aiming to evaluate the efficacy and safety of Sintilimab in the real world and explore the factors affecting the efficacy.

2. Materials And Methods

2.1. Research objects

Clinical data of patients with relapsed refractory lymphoma admitted to Shandong Cancer Hospital from February 2019 to April 2020 who received Sintilimab based treatment. Inclusion criteria: ① Lymphoma confirmed by pathological diagnosis; ② All patients had recurrent or refractory lymphoma; ③ Receive the treatment based on Sintilimab, and use Sintilimab more than once; ④ the safety of patients can be evaluated. Exclusion criteria: ① Unclear pathological diagnosis; ② Does not meet the definition criteria for recurrent or refractory lymphoma; ③ Incomplete clinical data; ④ the safety of patients cannot be evaluated.

Recurrent lymphoma is a type of lymphoma that recurs after a complete response to initial chemotherapy. Patients with refractory lymphoma were defined as those who met one of the following four criteria: ① Tumor reduction $\geq$ 50% or disease progression after 4 courses of standardized chemotherapy with standard regimen; ② Complete response (CR) was achieved by standard chemotherapy, but recurred within half a year; ③ Recurrence 2 or more times after CR; ④ Recurrence after hematopoietic stem cell transplantation.

Enrolled patients received Sintilimab (200 mg iv, once every 3 weeks) either as a single drug or in combination with chemotherapy/targeted therapy/radiotherapy. Efficacy was assessed every 2–4 cycles. Treatment until disease progression (PD), intolerance, or death.

2.2. Data acquisition

Clinical data of patients with relapsed or refractory lymphoma were collected, including clinicopathological characteristics, previous treatment regimen and efficacy, Sintilimab based treatment regimes, laboratory and imaging findings, therapeutic efficacy and adverse reactions.

2.3. Evaluation of curative effect and adverse reaction

The efficacy evaluation was divided into imaging response (CT/MRI) and metabolic response (PET/CT) according to the criteria revised in Lugano 2014[6]. Objective response rate (ORR) is the proportion of CR and partial response (PR) patients. Disease control rate (DCR) was the proportion of CR + PR + SD patients. The progression free Survival (PFS) is the interval between the onset of treatment and the first occurrence of PD or death from any cause. The clinical benefit rate (CBR) was CR + PR + SD for more than 6 months.

Adverse events were determined in accordance with the NCI term for Adverse events (CTCAE) [7]. Adverse events refer to any adverse or unexpected symptoms, signs, or diseases that are time-related to the medical treatment or procedure performed. Adverse events are classified as 1–5, with 5 being death.

2.4. Statistical analysis

The clinical and pathological characteristics of the patients were evaluated by descriptive analysis using SPSS 22.0 statistical analysis software. The 6-month progression-free survival rate was evaluated by Kaplan-Meier method and the survival curve was generated. In the efficacy analysis, chi-square test was used between dichotomous variables, rank sum test of multiple groups of independent samples was used between multiple grade variables, t-test was used between classified variables and continuous variables, and $P \leq 0.05$ was statistically significant.

3. Results

3.1. Clinical and pathological features of the patient

A total of 25 patients were collected for this analysis, all of whom had recurrent or refractory lymphoma. The median age of patients was 54 years (range 18–88 years). The ratio of males to females is 17:9.9 patients (36%) had extranodal infiltration of lesions with 2 or more, among which the most frequently infiltrated organs were bone and lung (7), followed by liver infiltration (5). Before the treatment with Sintilimab, the chemotherapy line was 1–6 lines (median was 3 lines), among which 22 patients (88%) had received chemotherapy at least 2 lines. 16 patients (64%) had received radiotherapy. The specific clinicopathological features of the patients are shown in Table 1 (At the end of the document).

Table 1
Pathological and clinical features of 25 patients

Patient characteristics	n (%)
Gender	
Male	16(64)
Female	9(36)
Age	
Median (range)	54(18–88)
≤ 60 (years)	15(60)
> 60 (years)	10(40)
Basic disease ¹	
Yes	13(52)
No	12(48)
Bad habits	
A history of smoking or drinking	7(28)
Non-smokers drink alcohol	18(72)
Extracapsular extension	
Yes	20(80)
No	5(20)
Body mass index(BMI) ²	
Overweight(BMI ≥ 25)	7(28)
Non-overweight(BMI<25)	18(72)
Pathological classification	
HL	12(48)
NHL ³	13(52)
B symptoms	
Yes	10(40)
Note: 1. Basic diseases include: coronary atherosclerosis, hypertension, diabetes, hepatitis. 2. Body mass Index (BMI) was calculated using weight/height ² . 3. There were 5 cases of non-Hodgkin's lymphoma including diffuse large B-cell lymphoma (DLBCL), 5 cases of extranodal NK/ T-cell lymphoma, 2 cases of granuloma fungoides and 1 case of enteropathy-related T-cell lymphoma.	

Patient characteristics	n (%)
No	15(60)
Clinical stages	
I-III	7(28)
IV	18(72)
Previous treatment	
Number of lines of chemotherapy	
1–2 lines	9(36)
3–4 lines	10(40)
5–6 lines	6(24)
He/she had been treated with radiation	16(64)
Efficacy after first-line treatment	
CR	6(24)
PR	12(48)
SD	2(8)
PD	5(20)
A treatment regimen based on Sintilimab	
Use Sintilimab alone	13(52)
The Sintilimab combination chemotherapy/targeted therapy	8(32)
The Sintilimab combination targeted therapy	4(16)
Status of Sintilimab therapy	
Stop the Sintilimab treatment	13(52)
Continue the Sintilimab treatment	12(48)
Number of Sintilimab treatments received	
1–4 times	10(40)
5–8 times	6(24)

Note: 1. Basic diseases include: coronary atherosclerosis, hypertension, diabetes, hepatitis. 2. Body mass Index (BMI) was calculated using weight/height². 3. There were 5 cases of non-Hodgkin's lymphoma including diffuse large B-cell lymphoma (DLBCL), 5 cases of extranodal NK/ T-cell lymphoma, 2 cases of granuloma fungoides and 1 case of enteropathy-related T-cell lymphoma.

Patient characteristics	n (%)
9–12 times	3(12)
13–18 times	6(24)
Whether efficacy can be assessed	
Yes	19(76)
No	6(24)
Note: 1. Basic diseases include: coronary atherosclerosis, hypertension, diabetes, hepatitis. 2. Body mass Index (BMI) was calculated using weight/height ² . 3. There were 5 cases of non-Hodgkin's lymphoma including diffuse large B-cell lymphoma (DLBCL), 5 cases of extranodal NK/ T-cell lymphoma, 2 cases of granuloma fungoides and 1 case of enteropathy-related T-cell lymphoma.	

3.2. Efficacy

At the end of follow-up, treatment was completed in 13 cases, treatment continued in 12 cases, and efficacy was evaluable in 19 cases, with one death due to an off-treatment event. (Figs. 1)

The median follow-up of 19 patients with evaluable efficacy was 9 months (3–16 months), the median duration of treatment with Sintilimab was 8 months (range 2–18), and the median duration of treatment with Sintilimab was 8 months (1.5–15 months).

The ORR and DCR of the patients were calculated based on the imaging evaluation after 4 cycles of treatment. Among the 19 patients, ORR, DCR and CBR were 63.2%, 84.2% and 73.7% respectively (Table 2). The risk-free survival (PFS) proportion of the patients is shown in Fig. 2. The PFS of 19 patients in 6 months was 73.7%.

13 of the 19 patients (68.4%) were treated with Sintilimab alone, ORR was 53.8%, DCR 84.6%, and CBR 84.6%. The ORR of the Sintilimab combined chemotherapy was 100%. The ORR of patients with Sintilimab combined with radiotherapy was 66.7%.

Among the 19 patients, 9 (47.4%) had Hodgkin lymphoma, 77.8% ORR, 100% DCR, and 100% CBR. There were 10 patients (52.6%) with non-Hodgkin lymphoma, ORR (50%) and CBR (50%). Among the 10 patients with non-Hodgkin's lymphoma, diffuse large B-cell lymphoma was found in 4 patients, with an ORR of 25% and a CBR of 0%. There were 6 patients with peripheral T/NK cell lymphoma, ORR was 66.7%, CBR was 83.3%. Different pathological types were associated with prognosis ($P = 0.002$) (appendix). The proportion of disease-free survival (PFS) across different pathologic types of lymphoma is shown in Fig. 3.

Table 2
Short-term efficacy and subgroup analysis of 19 patients with evaluable efficacy

	n (%)	response evaluation n (%)				ORR	DCR	CBR
		CR	PR	SD	PD	n (%)	n (%)	n (%)
totality	19 (100)	1 (5.3)	11 (57.9)	4 (21.0)	3 (15.8)	12 (63.2)	16 (84.2)	14 (73.7)
A treatment regimen based on Sintilimab								
Use Sintilimab alone	13 (68.4)	1 (7.7)	6 (46.1)	4 (30.8)	2 (15.4)	7 (53.8)	11 (84.6)	11 (84.6)
The Sintilimab combination chemotherapy/targeted therapy	3 (15.8)	0 (0)	3 (100)	0 (0)	0 (0)	3 (100)	3 (100)	2 (66.7)
The Sintilimab combination targeted therapy	3 (15.8)	0 (0)	2 (66.7)	0 (0)	1 (33.3)	2 (66.7)	1 (33.3)	1 (66.7)
Pathological classification								
HL	9 (47.4)	1 (11.1)	6 (66.7)	2 (22.2)	0 (0)	7 (77.8)	9 (100)	9 (100)
NHL	10 (52.6)	0 (0)	5 (50)	2 (20.0)	3 (30.)	5 (50.0)	7 (70.0)	5 (50.0)
DLBCL	4 (40.0)	0 (0)	1 (25.0)	0 (0)	3 (75.0)	1 (25.0)	1 (25.0)	0 (0)
Peripheral and cutaneous T-cell lymphomas	6 (60.0)	0 (0)	4 (66.7)	2 (33.3)	0 (0)	4 (66.7)	6 (100)	5 (83.3)

In the preset subgroup analysis, related to the recent curative effect in patients with prior chemotherapy line ($P = 0.029 \leq 0.05$), but the following factors had no relationship with the recent effect ($P \geq 0.05$): treatment, gender, age, B symptoms, Clinical stages, body mass index (BMI), β_2 MG, neutrophil to lymphocyte ratio(NLR), platelet to lymphocyte ratio(PLR), lymphocyte to monocyte ratio(LMR), if ever before radiotherapy, whether anemia, whether have hypothyroidism after the treatment (appendix, Table A1).

3.3. Safety

A total of 25 patients were available for safety analysis, of which 19 (76%) had treatment-related adverse events, most of which were level 1 and 2, and 5 (20%) of the 25 patients had level 3 or 4 adverse events. But no patients had grade 5 adverse reactions. Grade 3 or 4 adverse reactions occurred in patients after combination chemotherapy (gemcitabine or oxaliplatin or interferon) or targeted drugs (Chidamide and MabThera) with Sintilimab. The most common adverse reaction in 25 patients was hypothyroidism (n = 10;40%), anemia (n = 10; Decreased platelet count (n = 9;36%) and decreased neutrophil counts (n = 9;36%). See Table 3 for details. Among them, hypothyroidism is related to gender (P = 0.046) (appendix, Table A2). Hypothyroidism usually occurs within 5 cycles.(one medication cycle of 9 patients with curative effect evaluation for PR, drug withdrawal by developed progressive numbness of limbs weakness, four months after discontinuation of death, for the follow-up for patients with limb numbness sluggish examination and the treatment is unknown, can't determine whether caused by Sintilimab, so temporarily don't put it in the safety analysis of this observational study, here for a short description).

Table 3
Adverse events in 25 patients

	Adverse events (n = 25)				total
	Grade 1	Grade 2	Grade 3	Grade 4	
Hypothyroidism	10(40)	0	0	0	10(40)
Anemia	2(8)	6(24)	2(8)	0	10(40)
Decreased platelet count	4(16)	3(12)	2(8)	0	9(36)
Decreased neutrophil count	1(4)	5(20)	1(4)	2(8)	9(36)
Blood bilirubin is elevated	1(4)	1(4)	0	0	2(8)
Increased alanine aminotransferase	0	1(4)	0	0	1(4)
Increased aspartate aminotransferase	1(4)	0	0	0	1(4)
hypoalbuminemia	1(4)	0	1(4)	0	2(8)
pruritus	0	1(4)	0	0	1(4)

4. Discussion

In this real-world observational study based on the use of Sintilimab, Sintilimab demonstrated superior efficacy and safety. The ORR, DCR and CBR of the 19 patients were 63.2%, 84.2% and 73.7% respectively. This result is lower than the results of The Phase II study of Sintilimab [5] (ORR = 78.7%, DCR = 94.7%, CBR = 82.4%), considering that it is related to the pathological type of included patients. Only patients with relapsed or refractory classic Hodgkin's lymphoma were included in the phase II clinical trial. In our subgroup analysis of lymphoma types, ORR and DCR of Hodgkin's lymphoma were 77.8% and 100%, which were close to the results of the phase II clinical trial with Sintilimab. In the peripheral T/NK cell lymphoma subgroup, ORR and CBR were 66.7% and 83.3% respectively. This has not been reported in

previous literature, but in the 2019 ASCO meeting, the pathologic diagnosis of failure in asparaginase based regimen was extranodal NK/T cell lymphoma, nasal type (ENKTL). This result is similar to our observation.

The results of this observation suggest that Sintilimab has different curative effects in different pathological types. Efficacy was best in relapsed refractory Hodgkin's lymphoma (CBR = 100%), followed by peripheral T/NK cell lymphoma (CBR = 83.3%) and worst in diffuse large B cell lymphoma (CBR = 0%). This is similar to the efficacy reported by other anti-PD-1 [8–11]. The efficacy of Sintilimab in non-Hodgkin's disease needs to be confirmed in large cohort studies. A high response rate to anti-PD-1 in classic Hodgkin's lymphoma was associated with stronger expression of PD-L1 / PD-L2, which was due to amplification of 9p24.1 (sites of PD-L1, PD-L2 and JAK2 genes on chromosome 9) [12]. Genetic alterations in 9p24.1 are rare in DLBCL, and the incidence and severity of 9p24.1 alterations in DLBCL are significantly lower than those in cHL, as confirmed in a single-arm phase II study of Nivolumab for recurrent/refractory diffuse large B-cell lymphoma in patients who are not suitable or have failed autologous transplantation[9]. A retrospective analysis of 1253 biopsy samples from patients with DLBCL has proved that only 11% of them are PD-L1 positive [13]. Han et al. found that PD-L1 and PD-L2 showed higher expression levels in T cell lymphoma than in B cell lymphoma[14]. Jo et al. performed PD-1 and PD-L1 immunostaining on 79 ENKTL biopsy samples, and the expression rate of PD-L1 in ENKTL was as high as 79.7% [15].

Interestingly, it was observed in this study that the efficacy of Sintilimab was correlated with the number of previous chemotherapy lines ($P = 0.029$), and the lower the number of previous chemotherapy lines, the better the efficacy of Sintilimab. This is different from the results in the Phase II trial of Orient-1 Sintilimab[5], in which all included patients benefited to a similar degree from Sintilimab regardless of their previous chemotherapy regimen. It is worth noting that the refractory patients did not progress faster or worse even after receiving Sintilimab treatment [16]. It is different from the previous research results may be the reason; Sintilimab previous studies were limited to patients with cHL and this study included not only cHL but also NHL. Current studies have found that the expression level of PD-1 is weakened by chemotherapy, and chemotherapy may change the tumor antigen-specific response.

In the subgroup analysis of the choice of regimen for Sintilimab, there was no statistical difference between regimen and efficacy. This may be due to the small sample size, or it may be the case. This needs to be verified in future clinical trials of Sintilimab. Although some basic experimental studies suggest that chemotherapy [17] or radiotherapy [18, 19] can induce the up-regulation of PD-L1 expression in tumor cells, the percentage of PD-L1 expression in NSCLC cells after radiotherapy is significantly lower than that before radiotherapy[20]. Radiotherapy can induce tumor microenvironment sensitivity to immune checkpoint inhibitors[21]. Preclinical evidence [22, 23] shows that combining radiotherapy with anti-PD-1 therapy can improve the anti-tumor activity and long-term survival rate of the two treatments. In refractory Hodgkin's lymphoma, local irradiation combined with anti-PD-1 checkpoint blocking therapy has a synergistic effect [24]. Many other retrospective case series support a combined strategy of radiotherapy and anti-PD-1 / PD-L1 antibody therapy, including concurrent and sequential use, although

the exact mechanisms that contribute to improved outcomes are unclear. The synergetic effect of chemotherapy drugs and PD-1 antibody was also tested in a single-center, two-arm, open-label phase II clinical trial recently conducted by the PLA General Hospital [25]. The 6-month sustained response rate was 76% for Camrelizumab monotherapy, and 100% for Decitabine combined treatment with Camrelizumab.

In the analysis of influencing factors affecting the efficacy of PD-1 inhibitors, a retrospective study showed that PFS and OS of patients with BMI ≥ 25 were significantly longer than those with BMI ≤ 25 in continuous use of PD-1/PD-L1 inhibitors [26]. The reason may be that white adipose tissue also participates in the induction and/or coordination of host defense and is a source of cytokines and chemokines [27]. However, in this study, there was no statistical difference between BMI and efficacy, which may be related to the small sample size.

In this study, the most common adverse reactions were hypothyroidism (40%) and anemia (40%), and the adverse reactions were controllable. In this study, patients with grade 2 or 3 anemia had anemia prior to treatment, or were associated with combination of Sintilimab with radiotherapy or chemotherapy or targeted therapy. Our study found that the duration of hypothyroidism was within 5 cycles of treatment. Barroso et al recommend monitoring thyroid stimulating hormone and free thyroxine levels before each infusion of checkpoint inhibitors for at least the first five cycles of treatment [28]. The most common adverse reactions in the phase II clinical trial of Sintilimab were fever (41%) and hypothyroidism (22%). The overall tolerance of PD-1/PD-L1 inhibitors was superior to chemotherapy. PD-1 /PD-L1 inhibitors are associated with a lower risk of treatment-related symptoms (fatigue, anorexia, nausea, diarrhea, constipation, and sensory neuropathy), but a higher risk of immune-related adverse events [29]. It is worth noting that anti-PD-1 drugs can achieve long-term tumor control by prolonging immune activation, so immune-related adverse events requiring treatment may persist, develop or even occur over time [30]. As the use of anti-PD-1 drugs increases, there is a growing need for non-oncologists to manage rare but clinically significant organ-specific immune-related adverse events and more common general adverse events related to immune activation. A multidisciplinary clinical team may better meet the long-term needs of these patients.

5. Conclusions

In real-world studies, Sintilimab has been shown to be effective in recurrent or refractory lymphomas, especially in Hodgkin's lymphoma and T/NK cell lymphoma, with controlled adverse reactions.

6. Abbreviations

ORR: objective response rate; DCR: disease control rate; CBR: clinical response rate; PD1: programmed cell death protein 1; PD-L1: Programmed cell death 1 ligand 1; ML: malignant lymphoma; HL: Hodgkin's lymphoma; NHL: non-Hodgkin's lymphoma; DLBCL: diffuse large B-cell lymphoma; cHL: classical Hodgkin lymphoma; mAb: monoclonal antibody; CR: complete response; PR: partial response; SD: stable

disease; PD: progression disease; PFS: progression free Survival; BMI: Body Mass Index; OS: overall survival; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to Lymphocyte Ratio; LMR: lymphocyte to monocyte ratio; ENKTL: extranodal NK/T cell lymphoma, nasal type; PLA: Chinese People's Liberation Army

Declarations

Author Contributions

Conceptualization, Z-B x. and S-L h.; methodology, Q J.; software, M J.; validation, Q J., L-Q r and L-Q y.; formal analysis, Q J.; investigation, B B; resources, F S.; data curation, Q J.; writing—original draft preparation, Q J.; writing—review and editing, S-L h and Z-B x.; supervision, S-L h.; project administration, S-L H and M J.; funding acquisition, B B. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was ethically approved by the Medical Ethics Review Committee of Shandong Cancer Hospital, and the consent of each participant was obtained.

Consent for publication

Not applicable.

Competing interests

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Appendix

Table A1, The relationship between clinicopathological types and curative effect

	Efficacy(case)			P
Pathological type	CR+PR+SD	PD		
HL	9	0		
DLBCL	1	3		0.002
T/NK	6	0		
Number of previous chemotherapy lines	CR+PR	SD	PD	
1-2 lines	3	3	2	
3-4 lines	4	1	1	0.029
5-6 lines	5	0	0	
A treatment regimen based on Sintilimab				
Use Sintilimab alone	8	4	2	
The Sintilimab combination chemotherapy/targeted therapy	3	0	0	0.668
The Sintilimab combination targeted therapy	1	0	1	
β₂MG	11	4	3	0.561
NLR	11	4	3	0.568
PLR	11	4	3	0.901
LMR	11	4	3	0.221
BIM	12	4	3	0.322
≥25	7		0	0.161
<25	9		3	
Hypothyroidism after treatment				
Yes	5	2	1	0.963
No	7	2	2	
Anemia prior to treatment	11	4	3	0.173
Yes	6	1	3	0.590
No	5	3	0	
He/she had been treated with radiation				
Yes	8	3	1	0.538
No	4	1	2	

Gender				
Male	9	3	2	0.836
Female	3	1	1	
Age(year)				
≤60	8	3	0	0.163
>60	4	1	3	
B symptoms				
No	6	3	3	0.104
Yes	6	1	0	
Clinical stages				
I-III	4	1	0	0.306
IV	8	3	3	

Table A2. The relationship between hypothyroidism and clinical characteristics References

	Hypothyroidism occurs	No hypothyroidism occurred	P
Male	4	12	0.046
Female	6	3	
B symptoms	2	8	0.102
A symptom	8	7	
Use Sintilimab alone	4	9	0.337
The Sintilimab combination therapy	6	6	

Figures

(a)

(b)

Figure 1

(a) Represents 19 patients with evaluable efficacy. Different pathologic types were used currently using the Sintilimab cycle number and efficacy. (b) Represents the number of cycles and efficacy of 25 patients currently using Sintilimab, with the orange lines representing patients only for safety but not for efficacy. The following is an explanation of the legend: $\gg$ It stands for continued medication. $\diamond$ It stands for end of medication. $\square$ It stands for SD. $\bullet$ It stands for PD. $\triangle$ It stands for CR. $\blacksquare$ It represents death.

Figure 2

The proportion of 19 patients with disease-free survival

Figure 3

Comparison of disease-free survival rates among different pathological types.