Tislelizumab with gemcitabine and oxaliplatin in patients with relapsed or refractory classic Hodgkin lymphoma: a multicenter phase II trial

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Abstract

Although classic Hodgkin lymphoma (cHL) is highly curable with current treatment paradigms, therapy fails in 10-25% of patients. This prospective multicenter phase II study attempted to investigate the efficacy and safety of the combination of tislelizumab with gemcitabine and oxaliplatin (T-GemOx) in relapsed or refractory cHL. Participants received six to eight courses of gemcitabine (1 g/m^2 on day 1) and oxaliplatin (100 mg/m^2 on day 1) combined with tislelizumab (200 mg on day 2) at 21-day intervals, followed by tislelizumab maintenance (every 2 months for 2 years). The main outcome measure was the best complete remission rate. As of August 2022, a total of 30 patients had been consecutively enrolled and given induction therapy. The best overall response rate and complete remission rate were 100% (95% confidence interval [CI]: 88.4-100%) and 96.7% (95% CI: 82.8-99.9%), respectively. The median duration of follow-up after initiation of T-GemOx was 15.8 months. The 12-month progression-free survival rate without autologous stem cell transplant was 96% (95% CI: 74.8-99.4%). There were 122 adverse events recorded, of which 93.4% were grade 1 or 2. Thrombocytopenia (10%) and anemia (6.7%) were the most common grade 3 or 4 adverse events. Overall, T-GemOx demonstrated promising antitumor activity with manageable toxicities as a salvage treatment for relapsed or refractory cHL. A longer follow-up duration is required to determine whether maintenance therapy with tislelizumab rather than transplantation can be curative following such a highly active regimen. This trial was registered with the Chinese Clinical Trials Registry (*http://www.chictr.org.cn*) on June 1, 2020, identifier ChiCTR2000033441.

Introduction

Classic Hodgkin lymphoma (cHL) is one of the most common lymphoid neoplasms in adolescents and young adults, affecting 2-3 people per 100,000 per year.[1] Multiagent chemotherapy with or without radiation is frequently used as the first-line treatment for cHL, with 5-year survival rates of approximately 90% and 80% for early- and late-stage patients, respectively.[2-4] However, despite the high cure rate of cHL, approximately 10–25% of patients will have refractory disease or relapse after achieving remission.[1] Designing effective regimens for relapsed or refractory cHL (R/R cHL) is essential yet challenging.

Immune dysfunction is increasingly recognized as a crucial factor underlying the R/R status in patients with cHL. As a result of alterations in chromosome 9p24.1, Hodgkin Reed–Sternberg cells express high levels of programmed death ligand-1 (PD-L1) and PD-L2, which engage programmed death-1 (PD-1)-positive T cells and result in T-cell exhaustion, thereby enabling tumor cells to evade immune surveillance.[5-7] The anti-PD-1 antibodies nivolumab and pembrolizumab have been reported to produce a striking overall response rate (ORR) in patients with R/R

cHL.[8,9] However, the complete remission rate (CRR) was less than 30%, and most patients experienced recurrence or progression within 18 months.[8-9] Tislelizumab, a new, fully humanized immunoglobulin G4 monoclonal anti-PD-1 antibody, was designed to minimize binding to the Fcγ receptors on macrophages to avoid antibody-dependent cellular phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy.[10,11] Given its specific binding to the PD-1 CC'-loop and modification of the Fc fragment, tislelizumab has a higher affinity and slower dissociation than other anti-PD-1 antibodies.[12-14] Although lacking head-to-head comparisons, the reported CRR of tislelizumab monotherapy is numerically higher (62.9%) than that of other PD-1 antibodies.[8,9,15-17]

Considering the promising outcomes of tislelizumab monotherapy, we designed a tislelizumab-based combinatorial regimen to maximize the response rates of patients with R/R cHL. Although the CRR of gemcitabine combined with oxaliplatin (GemOx) alone was only 37.5%, the two drugs can synergize with checkpoint inhibitors to enhance the immunogenic death of tumor cells and exhibit direct cytotoxic effects.[18-22] Additionally, the GemOx regimen frequently presented no cross-resistance to first-line drugs and no dose-dependent toxicities. Therefore, we conducted an investigator-initiated, open-label, prospective, single-arm, phase II study to investigate the efficacy and safety of a combination of tislelizumab with GemOx (T-GemOx) in patients with R/R cHL.

Methods

Patients

This study, which started in August 2020, was conducted at seven medical centers in China. It was approved by the Chinese Ethics Committee for Registering Clinical Trials (ChiECRCT20200186) (*Online Supplementary File S1*). The inclusion criteria were as follows: (i) male and female patients diagnosed with cHL according to the criteria of the World Health Organization classification; (ii) at least one prior treatment regimen; (iii) biopsy-proven recurrence or progression; (iv) Eastern Cooperative Oncology Group performance status of 0-2; (v) at least one measurable lesion; (vi) a life expectancy of at least 3 months; and (vii) adequate organ function. There were no age restrictions. *Online Supplementary Table S1* presents the exclusion criteria for participant selection. The trial was registered on the Chinese Clinical Trials Registry Platform (ChiCTR2000033441) and followed the principles of the Declaration of Helsinki. All participants or parental guardians provided written informed consent to the study and its publication.

Procedures

The study was divided into two phases, i.e., the induction and maintenance phases. During the induction phase, all subjects received six to eight courses of gemcitabine 1 g/m^2 intravenously (IV) (day 1), oxaliplatin 100 mg/m^2 IV (day 1), and tislelizumab 200 mg IV (day 2) at 21-day intervals. The number of induction cycles was primarily influenced by the depth of remission in the first four courses. For complete responders, the planned induction therapy was six courses. The investigator had the option of adding up to two more courses. For partial responders, eight courses of T-GemOx were recommended. Following the completion of induction therapy, responders (patients who achieved a complete or partial remission) were continued into the maintenance phase (tislelizumab 200 mg IV at 2-month intervals) until disease progression, unacceptable toxicity, the patients' withdrawal, or the 2-year period of maintenance therapy had been completed. Concomitant therapies were administered for complications at the discretion of the treating physicians.

Study assessments

Tumor responses were categorized as positron emission tomography (PET) complete remission, partial remission, stable disease, and disease progression assessed by local investigators, according to the modified Lugano 2014 criteria. All patients underwent baseline PET scans before beginning the drug study, interim scans three to four courses into therapy, and restaging PET scans following completion of induction. During the maintenance phase, assessments were performed every 3 months in the first year and then every 6 months until 5 years of therapy. In the case of lack of efficacy or the patient withdrawing consent, an evaluation of efficacy outcomes was done in advance. The primary objective of this study was to identify the best CRR, defined as the percentage of patients who responded to treatment with best response being a complete remission. Secondary endpoints included the best ORR (complete plus partial remission), progression-free survival (time from study entry to disease progression or death), and safety profile. Safety was assessed by the frequency of adverse events (AE), graded per Common Terminology Criteria for Adverse Events, version 4.0.

Statistical methods

Sample size calculations were performed using PASS software (version 15.0.5). The study primarily aimed to evaluate the optimal CRR during T-GemOx treatment. The best CRR of tislelizumab monotherapy was 63%, which is higher than that of salvage combination chemotherapy (approximately 50%). Based on this, we assumed that the best CRR of T-GemOx, which was at least 88%, would be considered promising. Assuming a power of 80%, an α

value of 0.025 (one-sided), and an attrition rate of 20%, at least 30 patients would need to be enrolled in the study. Response rates were calculated using the Clopper-Pearson method and presented in proportions with the corresponding 95% confidence interval (95% CI). Survival was analyzed using a Kaplan-Meier plot. Quantitative variables were summarized as median and range whereas qualitative variables were described as counts and percentages. All *P* values were two-sided, and $P<0.05$ was considered statistically significant. Results were processed using R statistical software (version 4.1.0).

Results

Patients' characteristics

A total of 30 patients of the Chinese Han population were enrolled as of August 1, 2022. Figure 1 illustrates the patients' recruitment. All 30 patients completed induction therapy, and 26 patients received at least one maintenance dose of tislelizumab. Table 1 summarizes the patients' characteristics at study entry. The male:female ratio was 0.67. The median age was 33.5 years (range, 13-73 years), and no significant difference was observed between male and female patients (*P*=0.233). The predominant histological subtype was the nodular sclerosis type (70%). Advanced-stage disease was observed in 24 (80%) patients, three of whom exhibited bulky disease, with a mediastinal mass in two patients and retroperitoneal mass in one patient. All patients at the early stage belonged to an unfavorable-risk group (n=6, 20%) according to the German Hodgkin Study Group criteria. In patients with advanced-stage disease, seven (23.3%), seven (23.3%), and ten (33.3%) were in the low-intermediate, high-intermediate, and high-risk categories, respectively. Prior therapies are summarized in Table 2. All patients received doxorubicin, bleomycin, vinblastine, and dacarbazine as frontline therapy, of whom, ten (33.3%) attained

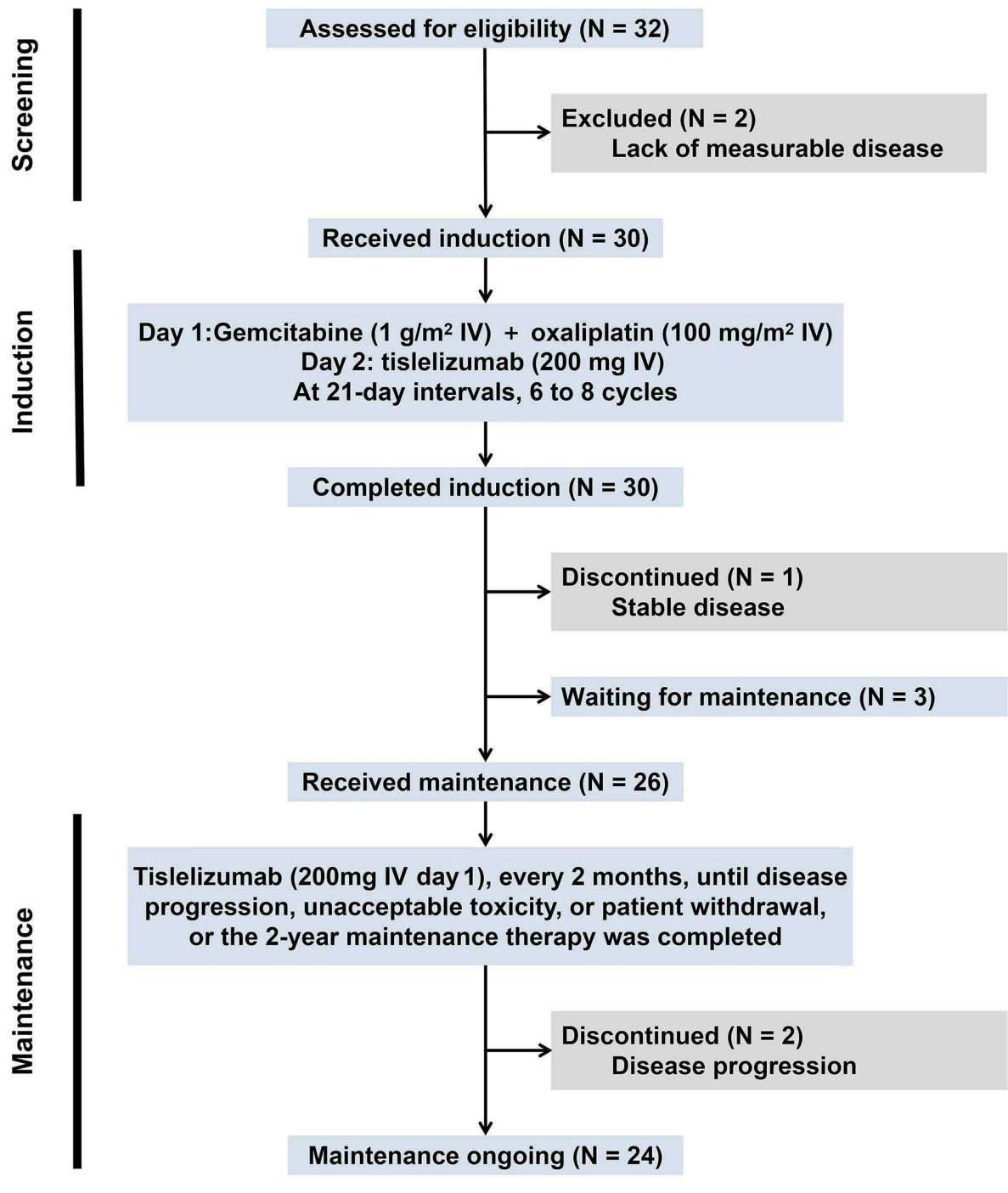

Figure 1. Flow diagram illustrating the enrollment of patients.

remissions before relapsing after a median time of response of 11.4 months. The remaining 20 patients (66.7%) exhibited primary refractory disease (no complete response to frontline therapy). During the subsequent treatment, five (16.7%) patients underwent autologous stem cell transplant (ASCT), two (6.7%) received brentuximab vedotin, four (13.3%) were treated with anti-PD-1 antibodies, and two (6.7%) received PD-L1 inhibitors. The ORR to the previous PD-1/PD-L1 inhibitors was 33.3% in our study; however, there were no complete responses. Approximately 30% of patients received three or more lines of prior therapies, and two-thirds were refractory to the most recent therapy.

Table 1. Patients' characteristics at study entry.

Characteristics	N=30
Age in years, median (range)	33.5 (13-73)
≤45 years, N (%)	20 (66.7)
>45 years, N (%)	10 (33.3)
Sex, N (%)	
Female	18 (60.0)
Male	12 (40.0)
Ethnic group, N (%)	
Han	30 (100.0)
Histological subtype, N (%)	
Nodular sclerosing cHL	21 (70.0)
Mixed cellularity cHL	6 (20.0)
Lymphocyte-depleted cHL	1 (3.3)
Lymphocyte-rich cHL	2 (6.7)
Ann Arbor stage, N (%)	
II	6 (20.0)
III	13 (43.3)
IV	11 (36.7)
Bulky mass*, N (%)	
No	27 (90.0)
Yes	3 (10.0)
Risk stratification, N (%)	
Early unfavorable (GHSG)	6 (20.0)
Low-intermediate risk (IPS 2)	7 (23.3)
High-intermediate risk (IPS 3)	8 (26.7)
High risk (IPS 4-7)	9 (30.0)
Extranodal involvement, N (%)	
No	15 (50.0)
Yes	15 (50.0)
B symptoms, N (%)	
No	11 (36.7)
Yes	19 (63.3)
ECOG PS, N (%)	
0	10 (33.3)
1	13 (43.3)
2	7 (23.3)

*Bulky disease was defined as any single node/nodal mass ≥10 cm in diameter or a mediastinal mass ratio of 0.33. cHL: classic Hodgkin lymphoma; GHSG: German Hodgkin Lymphoma Study Group; IPS: International Prognostic Score; ECOG PS: Eastern Cooperative Oncology Group performance status.

Responses

The cutoff date for analysis was August 1, 2022. The duration and depth of responses are presented in a swimmer's plot (Figure 2A). The median number of induction treatment cycles completed was eight (range, 6-8), with 43.3% (n=13) of patients receiving fewer than eight courses. During the treatment course, the confirmed best ORR and CRR were 100% (95% CI: 88.4-100%) and 96.7% (95% CI: 82.8-99.9%), respectively. At the end of induction, the ORR was 96.7% (95% CI: 82.8-99.9%), with 93.3% of patients achieving complete remission (Figure 2B). Figure 3 depicts responses after four cycles of T-GemOx in each prespecified subgroup. Significance tests were not conducted because of the small sample sizes of the subgroups.

Table 2. Prior treatment characteristics.

Characteristics	N=30
Previous lines of therapy, N (%)	
1 prior line	17 (56.7)
2 prior lines	4 (13.3)
≥3 prior lines	9 (30.0)
Prior chemotherapy, N (%)	30 (100)
ABVD	30 (100)
BEACOPP	2 (6.7)
GDP	4 (13.3)
ICE	4 (13.3)
IGEV	3 (10.0)
GVD	2 (6.7)
Other	2 (6.7)
Prior radiotherapy, N (%)	4 (13.3)
Prior ASCT, N (%)	5 (16.7)
Prior brentuximab vedotin, N (%)	2 (6.7)
Prior PD-1 antibody, N (%)	4 (13.3)
Prior PD-L1 antibody, N (%)	2 (6.7)
Response to PD-1/PD-L1 antibody*, N (%)	
Partial remission	2 (33.3)
Stable disease	2 (33.3)
Disease progression	2 (33.3)
Disease status, N (%)	
Relapsed after first-line chemotherapy	10 (33.3)
Refractory to first-line chemotherapy	20 (66.7)
Refractory to the most recent therapy	20 (66.7)

*The denominator is the number of patients who received prior PD-1 and PD-L1 antibodies. ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, prednisone; GDP: gemcitabine, dexamethasone, cisplatin; ICE: ifosfamide, carboplatin, etoposide; IGEV: ifosfamide, gemcitabine, etoposide; GVD: gemcitabine, vinorelbine, doxorubicin; ASCT: autologous stem cell transplantation; PD-1: programmed death-1; PD-L1: programmed death ligand-1.

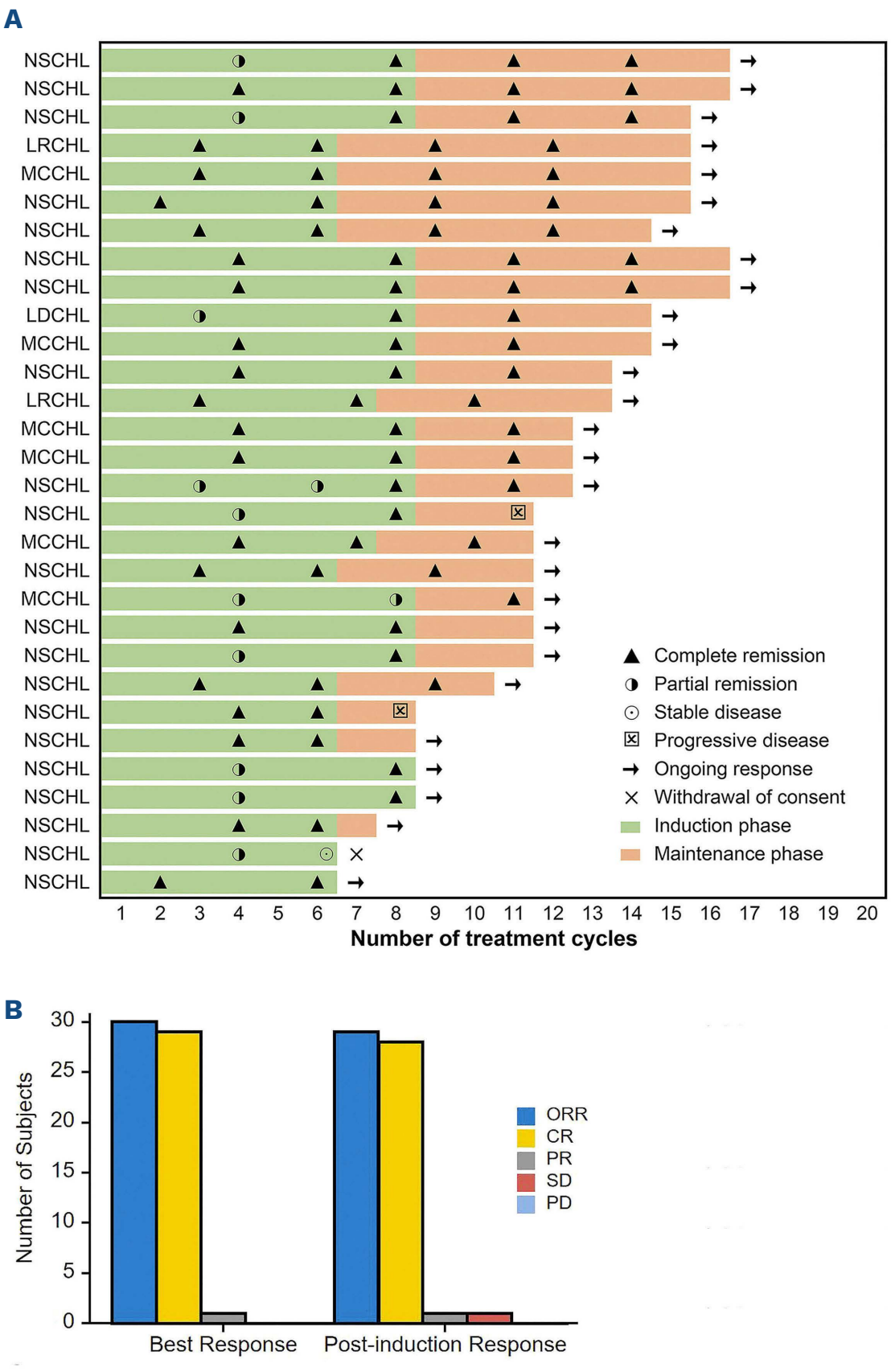

Figure 2. Efficacy following treatment with tislelizumab plus gemcitabine and oxaliplatin in patients with relapsed or refractory classic Hodgkin lymphoma. (A) Swimmer plot depicting individual patients as lines. (B) Therapeutic efficacy. NSCHL: nodular sclerosing classic Hodgkin lymphoma; LRCHL: lymphocyte-rich classic Hodgkin lymphoma; MCCHL: mixed cellularity classic Hodgkin lymphoma; LDCHL: lymphocyte-depleted classic Hodgkin lymphoma; ORR: overall response rate; CR: complete remission; PR: partial remission; SD: stable disease; PD: disease progression.

Two patients in the cohort exhibited disease progression following two and three cycles of tislelizumab maintenance, with remission durations of 6.8 and 10.4 months, respectively. Two other patients did not achieve complete remissions following induction therapy. These four patients had advanced-stage disease and belonged to the high-risk group. Although all of them had received one prior treatment regimen, three had primary refractory disease, and one had an early recurrence within a year.

Survival

The median duration of follow-up after initiation of T-GemOx was 15.8 months (range, 6.3-23.8 months). The median progression-free survival was not reached, and the 12-month progression-free survival rate was 96% (95% CI: 74.8-99.4%) (Figure 4). Among all responders, 80% and 56.7% had response durations of ≥6 months and ≥12 months, respectively. All patients survived until the last follow-up; however, overall survival data were not mature at the time of data cutoff.

Tolerability and safety

A total of 122 AE were recorded (Table 3), of which 114 (93.4%) were grade 1 or grade 2. Anemia (43.3%), pyrexia (40.0%), and fatigue (33.3%) were the most common grade 1 or 2 AE. Thrombocytopenia (10%) and anemia (6.7%) were

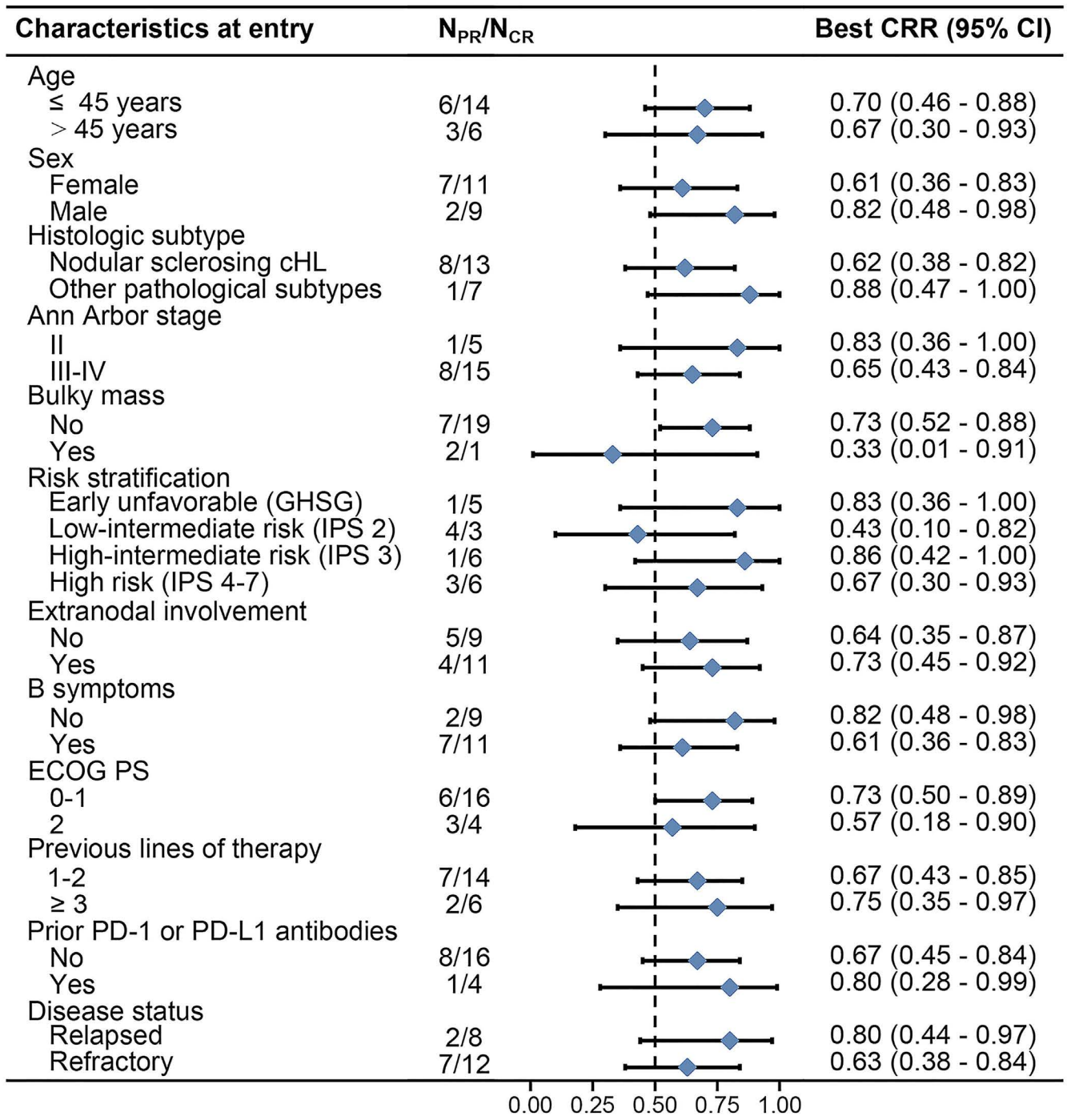

Figure 3. Responses after four cycles of tislelizumab with gemcitabine and oxaliplatin in each prespecified subgroup. One patient was excluded from this analysis as it was not possible to assess tumor response following the fourth cycle of tislelizumab plus gemcitabine and oxaliplatin. PR: partial remission; CR: complete remission; CRR: complete remission rate; 95% CI: 95% confidence interval; cHL: classic Hodgkin lymphoma; GHSG: German Hodgkin Lymphoma Study Group; IPS: International Prognostic Score; ECOG PS: Eastern Cooperative Oncology Group performance status; PD-1: programmed death-1; PD-L1: programmed death ligand-1.

the most common grade 3 or 4 AE. Grades 1-2 AE were generally tolerated whereas grades 3-4 AE were resolved with supportive care. No discontinuation caused by death or an AE was recorded.

As indicated in *Online Supplementary Table S2*, common immune-related AE included thyroid dysfunction (hypothyroidism, 30%; hyperthyroidism, 6.7%), rash (13.3%), and elevated transaminases (10%). Most immune-related AE were grade 1 or 2; only one was grade 3 in severity (elevated transaminase), which was treated with systemic steroids (prednisone), thus, contributing to treatment delays. Additionally, one patient experienced grade 1 cardiac toxicity (ventricular arrhythmias of unknown origin), which was considered immune-related. No endomyocardial biopsy or intervention was performed because of the pa-

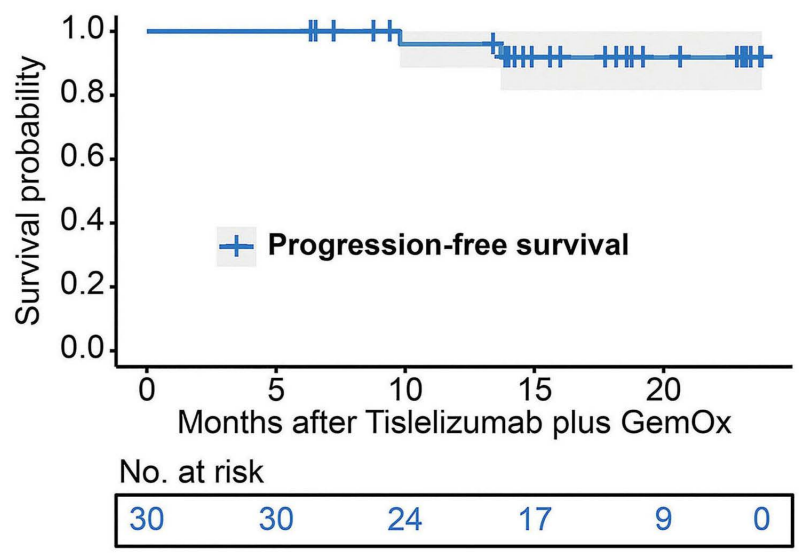

Figure 4. Kaplan-Meier curve for progression-free survival. GemOx: gemcitabine and oxaliplatin.

Table 3. Treatment-related adverse events.

Term	All grades N (%)	Grades 1-2 N (%)	Grades 3-4 N (%)
Anemia	15 (50.0)	13 (43.3)	2 (6.7)
Pyrexia	12 (40.0)	12 (40.0)	0
Fatigue	10 (33.3)	10 (33.3)	0
Poor appetite	9 (30.0)	9 (30.0)	0
Vomiting	9 (30.0)	9 (30.0)	0
Hypothyroidism	9 (30.0)	9 (30.0)	0
Nausea	8 (26.7)	8 (26.7)	0
Thrombocytopenia	7 (23.3)	4 (13.3)	3 (10.0)
Bacterial pneumonia	5 (16.7)	4 (13.3)	1 (3.3)
Rash	4 (13.3)	4 (13.3)	0
Neutropenia	4 (13.3)	3 (10.0)	1 (3.3)
Leukopenia	4 (13.3)	4 (13.3)	0
Proteinuria	3 (10.0)	3 (10.0)	0
Mucositis	3 (10.0)	3 (10.0)	0
Elevated transaminase	3 (10.0)	2 (6.7)	1 (3.3)
Pruritus	3 (10.0)	3 (10.0)	0
Hyperuricemia	3 (10.0)	3 (10.0)	0
Paresthesia	2 (6.7)	2 (6.7)	0
Hyperthyroidism	2 (6.7)	2 (6.7)	0
Diarrhea	2 (6.7)	2 (6.7)	0
Headache	2 (6.7)	2 (6.7)	0
Hematuria	1 (3.3)	1 (3.3)	0
Cardiac toxicity	1 (3.3)	1 (3.3)	0
Back pain	1 (3.3)	1 (3.3)	0

tient's continued asymptomatic presentation. Three patients had grade 2 hypothyroidism, and all remained stable on levothyroxine.

Discussion

This trial demonstrated that additional GemOx before tislelizumab further improved response rates, with the best ORR and CRR being improved to 100% and 96.7%, respectively. Theoretically, the sequence of drug administration (i.e., administering tislelizumab after GemOx) is essential for enhancing the impact of tislelizumab. It has been reported that increased circulating myeloid-derived suppressor cells in cHL were associated with poor efficacy, early progression, and resistance to checkpoint inhibitors.[19,20] Preclinical data have demonstrated that gemcitabine reduces the number of myeloid-derived suppressor cells, favoring the reprogramming of tumor-associated macrophages toward an immunostimulatory phenotype.[21,23] It can also stimulate histocompatibility complex-1 expression on tumor cells to increase their antigenicity.[24] Oxaliplatin promotes the activity of neutrophils and macrophages and the depletion of myeloid-derived suppressor cells.[22,25] Thus, the application of GemOx before tislelizumab may potentially contribute to improve tumor responses and reverse resistance. In practice, we demonstrated that patients who previously responded poorly to anti-PD-1 or anti-PD-L1 therapy achieved deep remissions after the administration of T-GemOx, suggesting that such a regimen may restore sensitivity to checkpoint inhibitors.

Similar to our work, other researchers have assessed combination regimens containing a PD-1 inhibitor to obtain better clinical efficacy.[26-30] A phase II PET-adapted study compared the efficacy of nivolumab monotherapy and nivolumab in combination with ifosfamide, carboplatin, and etoposide (NICE) and observed notably higher response rates in the NICE group than in the single-agent group (ORR 93% *vs*. 81%; CRR 91% *vs*. 71%).[26] Another phase II trial found that the CRR in patients naïve to PD-1 blockade was significantly higher in those treated with low-dose decitabine plus camrelizumab than in those treated with camrelizumab alone (71% *vs*. 32%).[30] Additionally, the CRR with gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) alone was approximately 50% whereas that with pembrolizumab plus GVD was 95%.[28] Our study demonstrated similar response rates, implying that the benefit of PD-1 blockade is greater when it is combined with other therapies.

From a safety standpoint, immunosuppressants such as cyclophosphamide and ifosfamide are not the best options as they may increase the risk of infections. Previously used medications, particularly anthracyclines and vincristine, may contribute to resistance and dose-dependent toxicities. Considering the aforementioned, we combined the GemOx regimen in this study. One of the expected challenges in developing combination therapies was increased toxicities, which might be resolved by reducing doses and/or increasing treatment intervals. GemOx alone was typically administered every 2 weeks, and tislelizumab monotherapy was typically administered every 3 weeks. To balance clinical benefit with toxicity, we did not change the dose of GemOx and extended its treatment interval appropriately to a 3-week course to synchronize the combination regimen. In all, the data suggested that T-GemOx was associated with a manageable safety profile.

Recent data suggest that treatment with PD-1 inhibitors may sensitize patients with chemorefractory cHL to subsequent high-dose chemotherapy and ASCT.[31] ASCT after PD-1-blockade has produced considerably favorable outcomes in multiple trials, with 2-year progression-free survival rates of 72-88%.[26,29] Nevertheless, these efficacy benefits must be considered in the context of relative safety profiles. One conference abstract from the 2022 European Hematology Association reported that the incidence of engraftment syndrome of ASCT following anti-PD-1 treatment was high (18.6%), which can cause fulminant immune-related AE (myocarditis and pneumonitis).[32] It must be noted that these findings were preliminary, and further research is required to confirm the safety of ASCT following anti-PD-1 treatment in the context of possible immune-related AE.

Previous data on anti-PD-1 monotherapy suggested that a subgroup of patients achieving an excellent response to PD-1 blockade remain disease-free for >3 years even after discontinuation of anti-PD-1 treatment and thus may be cured.[33] The therapeutic potential of anti-PD-1 combination regimens is under active study. Considering the high efficacy of our treatment combination, a challenge faced in this study was whether all patients required ASCT consolidation. In other words, can we now provide a path toward reducing the need for ASCT in the relapsed/refractory setting with secondary complete response status? The half-life of tislelizumab was 26 days following repeat administration in population pharmacokinetic analyses.[14] Thus, we are investigating a brief maintenance treatment of every 2 months for 2 years instead of transplantation. Our observed 12-month progression-free survival rate was 96%, and further follow-up is required to assess long-term outcomes.

Our study has certain limitations. First, all our subjects were Chinese, which may limit generalizability to other racial/ethnic groups. Second, the proportion of patients treated with brentuximab vedotin and ASCT in our study was relatively low compared to that in western countries, which can be attributed to country-specific differences in treatment landscapes. Third, a relatively short follow-up period and the small number of events limited the generalization of the findings. Last, the heterogeneity of the number of cycles received by patients was another potential limitation, adding to the challenge of establishing best practices.

In conclusion, our study illustrated that T-GemOx is a highly efficacious, less toxic, and cost-effective therapy in R/R cHL. This regimen can be completely implemented in the outpatient setting in the future because of the simple dosing strategy and favorable safety profile, thereby shortening hospital stays. It should be emphasized that it is premature to assess the durability of responses with tislelizumab maintenance. Longer follow-up and prospective controlled studies are required to investigate whether this transplant-free strategy can replace traditional consolidation with ASCT and whether T-GemOx can be used as a bridging therapy for patients who still need transplantation.

Disclosures

No conflicts of interest to disclose.

Contributions

LF and JL conceptualized and designed the study, supervised the data analysis, and reviewed and revised the manuscript critically. KD, HL, and JM acquired data, conducted statistical analyses, and drafted the paper. HY, LC, HW, HP, WS, XZ, WW, and HZ acquired data, helped to analyze and interpret the data, and reviewed and revised the manuscript. All authors approved the submitted and final versions.

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Data-sharing statement

The data generated in this study are available upon request from the corresponding author.

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