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Contents

Thrice Monthly Volume 9 Number 21 July 26, 2021

REVIEW

- 5754 Treatment strategies for hepatocellular carcinoma with extrahepatic metastasis
Long HY, Huang TY, Xie XY, Long JT, Liu BX

MINIREVIEWS

- 5769 Prevention of hepatitis B reactivation in patients requiring chemotherapy and immunosuppressive therapy
Shih CA, Chen WC
- 5782 Research status on immunotherapy trials of gastric cancer
Liang C, Wu HM, Yu WM, Chen W
- 5794 Therapeutic plasma exchange for hyperlipidemic pancreatitis: Current evidence and unmet needs
Zheng CB, Zheng ZH, Zheng YP
- 5804 Essentials of thoracic outlet syndrome: A narrative review
Chang MC, Kim DH

ORIGINAL ARTICLE

Case Control Study

- 5812 Soluble programmed death-1 is predictive of hepatitis B surface antigen loss in chronic hepatitis B patients after antiviral treatment
Tan N, Luo H, Kang Q, Pan JL, Cheng R, Xi HL, Chen HY, Han YF, Yang YP, Xu XY

Retrospective Cohort Study

- 5822 Tunneled biopsy is an underutilised, simple, safe and efficient method for tissue acquisition from subepithelial tumours
Koutsoumpas A, Perera R, Melton A, Kuker J, Ghosh T, Braden B

Retrospective Study

- 5830 Macular ganglion cell complex injury in different stages of anterior ischemic optic neuropathy
Zhang W, Sun XQ, Peng XY
- 5840 Value of refined care in patients with acute exacerbation of chronic obstructive pulmonary disease
Na N, Guo SL, Zhang YY, Ye M, Zhang N, Wu GX, Ma LW
- 5850 Facilitators and barriers to colorectal cancer screening in an outpatient setting
Samuel G, Kratzer M, Asagbra O, Kinderwater J, Poola S, Udom J, Lambert K, Mian M, Ali E
- 5860 Development and validation of a prognostic nomogram for colorectal cancer after surgery
Li BW, Ma XY, Lai S, Sun X, Sun MJ, Chang B

Observational Study

- 5873** Potential protein-phenotype correlation in three lipopolysaccharide-responsive beige-like anchor protein-deficient patients

Tang WJ, Hu WH, Huang Y, Wu BB, Peng XM, Zhai XW, Qian XW, Ye ZQ, Xia HJ, Wu J, Shi JR

- 5889** Quantification analysis of pleural line movement for the diagnosis of pneumothorax

Xiao R, Shao Q, Zhao N, Liu F, Qian KJ

Prospective Study

- 5900** Preprocedure ultrasound imaging combined with palpation technique in epidural labor analgesia

Wu JP, Tang YZ, He LL, Zhao WX, An JX, Ni JX

Randomized Controlled Trial

- 5909** Effects of perioperative rosuvastatin on postoperative delirium in elderly patients: A randomized, double-blind, and placebo-controlled trial

Xu XQ, Luo JZ, Li XY, Tang HQ, Lu WH

SYSTEMATIC REVIEWS

- 5921** Pain assessment and management in the newborn: A systematized review

Garcia-Rodriguez MT, Bujan-Bravo S, Seijo-Bestilleiro R, Gonzalez-Martin C

META-ANALYSIS

- 5932** Fatigue prevalence in men treated for prostate cancer: A systematic review and meta-analysis

Luo YH, Yang YW, Wu CF, Wang C, Li WJ, Zhang HC

CASE REPORT

- 5943** Diagnostic discrepancy between colposcopy and vaginoscopy: A case report

Li Q, Zhang HW, Sui L, Hua KQ

- 5948** Contrast enhanced ultrasound in diagnosing liver lesion that spontaneously disappeared: A case report

Wang ZD, Haitham S, Gong JP, Pen ZL

- 5955** COVID-19 patient with an incubation period of 27 d: A case report

Du X, Gao Y, Kang K, Chong Y, Zhang ML, Yang W, Wang CS, Meng XL, Fei DS, Dai QQ, Zhao MY

- 5963** Awake extracorporeal membrane oxygenation support for a critically ill COVID-19 patient: A case report

Zhang JC, Li T

- 5972** Meigs syndrome with pleural effusion as initial manifestation: A case report

Hou YY, Peng L, Zhou M

- 5980** Giant hemangioma of the caudate lobe of the liver with surgical treatment: A case report

Wang XX, Dong BL, Wu B, Chen SY, He Y, Yang XJ

- 5988** Anti-programmed cell death ligand 1-based immunotherapy in recurrent hepatocellular carcinoma with inferior vena cava tumor thrombus and metastasis: Three case reports
Liu SR, Yan Q, Lin HM, Shi GZ, Cao Y, Zeng H, Liu C, Zhang R
- 5999** Minimal deviation adenocarcinoma with elevated CA19-9: A case report
Dong Y, Lv Y, Guo J, Sun L
- 6005** Isolated fungus ball in a single cell of the left ethmoid roof: A case report
Zhou LQ, Li M, Li YQ, Wang YJ
- 6009** Rare case of brucellosis misdiagnosed as prostate carcinoma with lumbar vertebra metastasis: A case report
Yan JF, Zhou HY, Luo SF, Wang X, Yu JD
- 6017** Myeloid sarcoma of the colon as initial presentation in acute promyelocytic leukemia: A case report and review of the literature
Wang L, Cai DL, Lin N
- 6026** Primary follicular lymphoma in the renal pelvis: A rare case report
Shen XZ, Lin C, Liu F
- 6032** Rosai-Dorfman disease in the spleen of a pediatric patient: A case report
Ryu H, Hwang JY, Kim YW, Kim TU, Jang JY, Park SE, Yang EJ, Shin DH
- 6041** Relapsed/refractory classical Hodgkin lymphoma effectively treated with low-dose decitabine plus tislelizumab: A case report
Ding XS, Mi L, Song YQ, Liu WP, Yu H, Lin NJ, Zhu J
- 6049** Disseminated *Fusarium* bloodstream infection in a child with acute myeloid leukemia: A case report
Ning JJ, Li XM, Li SQ
- 6056** Familial hemophagocytic lymphohistiocytosis type 2 in a female Chinese neonate: A case report and review of the literature
Bi SH, Jiang LL, Dai LY, Wang LL, Liu GH, Teng RJ
- 6067** Usefulness of metagenomic next-generation sequencing in adenovirus 7-induced acute respiratory distress syndrome: A case report
Zhang XJ, Zheng JY, Li X, Liang YJ, Zhang ZD
- 6073** Neurogenic orthostatic hypotension with Parkinson's disease as a cause of syncope: A case report
Li Y, Wang M, Liu XL, Ren YF, Zhang WB
- 6081** SATB2-associated syndrome caused by a novel SATB2 mutation in a Chinese boy: A case report and literature review
Zhu YY, Sun GL, Yang ZL
- 6091** Diagnosis and treatment discussion of congenital factor VII deficiency in pregnancy: A case report
Yang Y, Zeng YC, Rumende P, Wang CG, Chen Y

- 6102** Unusual immunohistochemical “null” pattern of four mismatch repair proteins in gastric cancer: A case report
Yue M, Liu JY, Liu YP
- 6110** Generalized periodontitis treated with periodontal, orthodontic, and prosthodontic therapy: A case report
Kaku M, Matsuda S, Kubo T, Shimoe S, Tsuga K, Kurihara H, Tanimoto K
- 6125** Ligamentum flavum hematoma following a traffic accident: A case report
Yu D, Lee W, Chang MC
- 6130** Oral cyclophosphamide-induced posterior reversible encephalopathy syndrome in a patient with ANCA-associated vasculitis: A case report
Kim Y, Kwak J, Jung S, Lee S, Jang HN, Cho HS, Chang SH, Kim HJ
- 6138** Encapsulating peritoneal sclerosis in an AMA-M2 positive patient: A case report
Yin MY, Qian LJ, Xi LT, Yu YX, Shi YQ, Liu L, Xu CF
- 6145** Multidisciplinary diagnostic dilemma in differentiating Madelung’s disease – the value of superb microvascular imaging technique: A case report
Seskute G, Dapkute A, Kausaite D, Strainiene S, Talijunas A, Butrimiene I
- 6155** Complicated course of biliary inflammatory myofibroblastic tumor mimicking hilar cholangiocarcinoma: A case report and literature review
Strainiene S, Sedleckaite K, Jarasunas J, Savlan I, Stanaitis J, Stundiene I, Strainys T, Liakina V, Valantinas J
- 6170** Fruquintinib beneficial in elderly patient with neoplastic pericardial effusion from rectal cancer: A case report
Zhang Y, Zou JY, Xu YY, He JN

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Relapsed/refractory classical Hodgkin lymphoma effectively treated with low-dose decitabine plus tislelizumab: A case report

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Abstract

BACKGROUND

Academic studies have proved that anti-programmed death-1 (PD-1) monoclonal antibodies demonstrated remarkable activity in relapsed/refractory classical Hodgkin lymphoma (cHL). However, most patients ultimately experienced failure or resistance. It is urgent and necessary to develop a novel strategy for relapsed/refractory cHL. The aim of this case report is to evaluate the combination approach of low-dose decitabine plus a PD-1 inhibitor in relapsed/refractory cHL patients with prior PD-1 inhibitor exposure.

CASE SUMMARY

The patient was a 27-year-old man who complained of enlarged right-sided cervical lymph nodes and progressive pain aggravation of the right shoulder over the past 3 mo before admission. Histological analysis of lymph node biopsy was suggestive of cHL. The patient experienced failure of eight lines of therapy, including multiple cycles of chemotherapy, PD-1 blockade, and anti-CD47 antibody therapy. Contrast-enhanced CT showed that the tumors of the chest and abdomen significantly shrunk or disappeared after three cycles of treatment with decitabine plus tislelizumab. The patient had been followed for 11.5 mo until March 2, 2021, and no progressive enlargement of the tumor was observed.

CONCLUSION

The strategy of combining low-dose decitabine with tislelizumab could reverse the resistance to PD-1 inhibitors in patients with heavily pretreated relapsed/refractory cHL. The therapeutic effect of this strategy needs to be further assessed.

Key Words: Immunotherapy; Hypomethylating agent; Classical Hodgkin lymphoma; Survival; Case report

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Core Tip: We report a 27-year-old man who complained of enlarged right-sided cervical lymph nodes and progressive pain aggravation of the right shoulder over the past 3 mo before admission. Histological analysis of lymph node biopsy was suggestive of classical Hodgkin's lymphoma. The patient experienced failure of eight lines of therapy. Computed tomography showed that the tumors of the chest and abdomen significantly shrunk or disappeared after three cycles of treatment with low-dose decitabine plus tislelizumab. The patient had been followed for 11.5 mo until March 2, 2021, and no progressive enlargement of the tumor was observed.

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INTRODUCTION

Classical Hodgkin's lymphoma (cHL) is a largely curable malignancy of the lymphatic system. Patients with newly diagnosed cHL are often treated with empirical combination chemotherapy regimens, such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). Approximately 20% to 30% of patients will experience progression after treatment or fail to respond to induction therapy[1,2]. For these patients, < 20% were exposed to autologous stem-cell transplantation stem-cell transplantation (ASCT) and even fewer to brentuximab vedotin (BV) in China. In recent years, immune checkpoint inhibitors (ICIs) have provided very impressive results with prolonged remission or disease stabilization in many patients. Unfortunately, the majority of these patients will experience resistance or failure, and subsequent therapy is challenging[3,4]. Recently, clinical data found that resistance to ICIs may be reversed by hypomethylating agents, such as decitabine, in heavily pretreated cHL patients[5,6]. The aim of this case report is to evaluate the combination approach of low-dose decitabine plus a programmed death-1 (PD-1) inhibitor in relapsed/refractory cHL patients with prior PD-1 inhibitor exposure.

CASE PRESENTATION

Chief complaints

The patient was a 27-year-old man who complained of enlarged right-sided cervical lymph nodes and progressive pain aggravation of the right shoulder in 2014.

History of present illness

The patient's right-sided cervical lymph nodes appeared significantly enlarged approximately 3 mo before admittance, and lymph node biopsy was suggestive of cHL. The patient experienced failure of eight lines of therapy. The treatment procedure is provided in Table 1.

History of past illness

The patient was diagnosed with subclinical hypothyroidism in September 2018, and levothyroxine (25 µg/d) was prescribed at the Chinese People's Liberation Army General Hospital. The patient's family history was negative.

Personal and family history

Other symptoms were not present and the patient did not drink alcohol, smoke, or have a history of surgery.

Table 1 The entire treatment process after the diagnosis

Time of therapy	Treatment	Best efficacy	PFS (mo)
November 2014	ABVD × 6 cycles	CR	16
March 2016	AVD × 1 cycle	Unknown	-
September 2016	AVD × 1 cycle	Unknown	-
October 2016	GVD × 4 cycles	PD	4.8
October 2017	GVD × 6 cycles	SD	8.8
July 2018	ESHAP × 1 cycle	PD	0.9
October 2018	AK105 × 9 cycles	PR	3.5
July 2019	IBI188 × 16 wk	SD	3.6
November 2019	DICE × 2 cycles	PD	1.3
February 2020	F0002-ADC × 1 cycle	PD	0.6
March 2020	Decitabine plus tislelizumab	PR	11.5

PFS: Progression-free survival; CR: Complete remission; PR: Partial remission; PD: Progression disease; SD: Stable disease; ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD: Doxorubicin, vinblastine, and dacarbazine; GVD: Gemcitabine, vinorelbine, liposomal doxorubicin; ESHAP: Etoposide, methylprednisolone, high-dose cytarabine, and cisplatin; DICE: Dexamethasone, ifosfamide, cisplatin, and etoposide.

Physical examination

On admission, the patient's blood pressure was 120/74 mmHg, pulse rate was 80 beats/min, and temperature was 36.1 °C. His body weight was 77.5 kg, and his height was 172 cm (BMI 26.2 kg/m², body surface area). His performance status was 2 according to the criteria of the Eastern Cooperative Oncology Group, and his pain was 6 out of 10 according to the numeric rating scale (NRS). No superficial lymphadenopathy was noted. The left buttock was fuller than the right buttock, and no soft tissue tumor was palpated in the left buttock. Left hip tenderness was noted.

Laboratory examinations

On admission, routine blood tests revealed significant leukocytosis, moderate anemia, decreased albumin, and slightly elevated blood urea nitrogen. The patient's blood biochemical tests were indicative of impaired liver function with a slight elevation of alkaline phosphatase and glutamyl transferase levels. The coagulation function test showed a marked elevation in plasma fibrinogen and activated partial thromboplastin time levels. The results are presented in [Table 2](#).

Imaging examinations

A computed tomography (CT) scan of the chest revealed that multiple lung nodules significantly decreased or disappeared after treatment with three cycles of combination therapy of decitabine and tislelizumab ([Figure 1](#)). Similarly, a CT scan of the abdomen and pelvis showed that abdominal lymph nodes decreased in size ([Figure 2](#)).

FINAL DIAGNOSIS

The patient was finally diagnosed with cHL by biopsy of the right cervical lymph node. The subtype was nodular sclerosis, Ann Arbor stage IVB, involving the left iliac muscle, left piriformis muscle, sacrum, bilateral ilium, bone marrow, left supraclavicular lymph nodes, mediastinal lymph nodes, right hilar lymph nodes, retroperitoneal lymph nodes, and bilateral lymph nodes near iliac blood vessels. Immunohistochemistry revealed the following: CD15 (+), CD163 (-), CD3 (-), CD30 (+), EBER (-), EBV (-), EMA (-), Ki67 (+), LCA (-), PAX-5 (weakly +), CD20 (+), CD57 (-), ALK (-), and CD68 (-).

Table 2 Laboratory blood test results at hospital admission

	Result	Normal range
Hematology		
White blood cell count	$20.81 \times 10^9/L$	4.0-10.0
Red blood cell count	$3.17 \times 10^{12}/L$	3.5-5.5
Hemoglobin	87 g/L	120.0-160.0
Hematocrit	28.8%	37.0-49.0
MCV	91 fl	82.0-92.0
MCH	27.3 pg	27.0-31.0
MCHC	300 g/L	320.0-360.0
Platelets	$384 \times 10^9/L$	100.0-350.0
Lymphocytes	$0.96 \times 10^9/L$	1.0-5.0
Monocytes	$0.24 \times 10^9/L$	0.2-0.8
Neutrophils	$19.59 \times 10^9/L$	2.0-8.0
Eosinophils	$0 \times 10^9/L$	0.1-0.5
Basophils	$0.02 \times 10^9/L$	0.0-0.1
ESR		
Coagulation		
APTT	59.3 s	24.0-39.0
Thrombin time	16.6 s	14.0-21.0
Prothrombin time	12.6 s	11.0-14.0
INR	1.11	0.8-1.5
Prothrombin activity	81.9%	70.0-130.0
Fibrinogen	942.1 mg/dL	200.0-400.0
Biochemistry		
C-reactive protein	106.3 mg/L	< 8.0
Procalcitonin	0.47 ng/mL	< 0.5
Glucose	7.24 mmol/L	3.6-6.1
Creatinine	57 μ mol/L	50.0-130.0
MDRD GFR	> 60 mL/min	> 60
Uric acid	318 μ mol/L	90.0-420.0
Lactate dehydrogenase	260 IU/L	110.0-240.0
ALB	40.1 g/L	35.0-55.0
TP	69.4 g/L	60.0-80.0
Alkaline phosphatase	178 IU/L	40.0-160.0
Serum iron	9.9 μ mol/L	10.6-28.3
Serum ferritin	7585 μ g/L	30.0-400.0
UIBC	20 μ mol/L	19.7-66.2
TIBC	29.9 μ mol/L	40.8-76.6
Total cholesterol	4.66 mmol/L	2.84-5.68
Triglycerides	0.97 mmol/L	0.56-1.7
Hormones		
TSH	3.47 mIU/L	0.27-4.2

FT3	3.59 pmol/L	3.1-6.8
FT4	17.34 pmol/L	12.0-22.0
Electrolytes		
Sodium	137 mmol/L	135.0-145.0
Potassium	4.47 mmol/L	3.5-5.3
Calcium-total	2.35 mmol/L	2.12-2.75
Phosphates inorganic	0.83 mmol/L	0.69-1.6
Liver enzymes		
ALT	25 IU/L	0.0-40.0
AST	23 IU/L	0.0-45.0
GGT	151 IU/L	10.0-50.0
DBIL	3.0 μ mol/L	0.0-6.0
Total bilirubin	9.4 μ mol/L	1.7-20.0
Virology tests		
Anti-HCV	Negative	
HbsAg	Negative	
Anti-HIV	Negative	

MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; ESR: Erythrocyte sedimentation rate; APTT: Activated partial thromboplastin time; INR: International normalized ratio; MDRD GFR: Modification of diet in renal disease glomerular filtration rate; TP: Total protein; UIBC: Unsaturated iron binding capacity; TIBC: Total iron binding capacity; TSH: Thyroid stimulating hormone; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; DBIL: direct bilirubin; HbsAg: Surface antigen of hepatitis B virus; HCV: Hepatitis B virus; HIV: Human immunodeficiency virus.

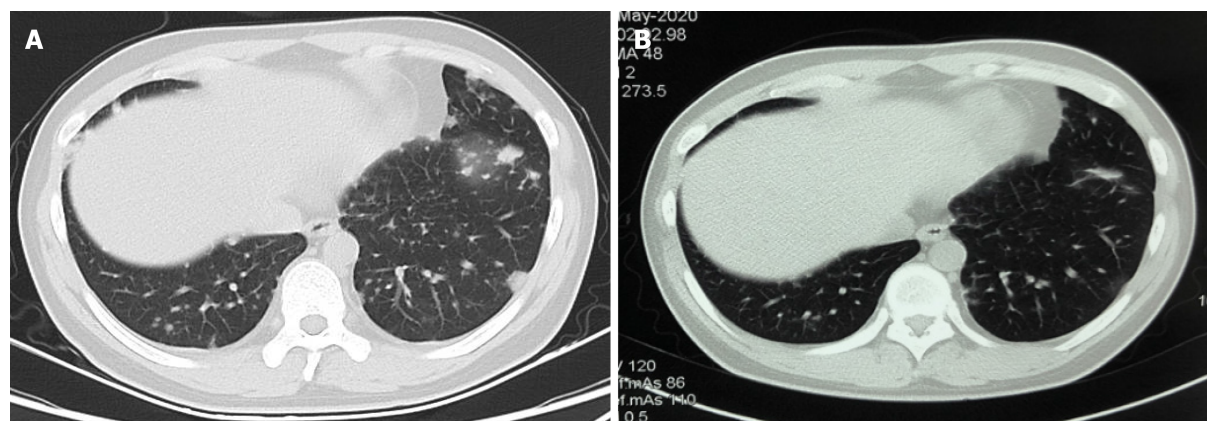


Figure 1 Computed tomography scan of the chest before and after combination therapy. A: Imaging features before treatment; B: Imaging changes after three cycles of treatment.

TREATMENT

The patient was treated with decitabine (10 mg/d, days 1 to 5) plus tislelizumab (200 mg, day 6) every 3 wk. A total of 12 courses of combination therapy were delivered.

OUTCOME AND FOLLOW-UP

To date, the patient has completed 12 cycles of decitabine in combination with the PD-1 inhibitor tislelizumab, and the date of the last cycle was November 17, 2020. Abdominal pain was significantly alleviated, and the NRS score decreased to 1 to date. Partial remission was achieved after treatment until March 2, 2021, and progression-

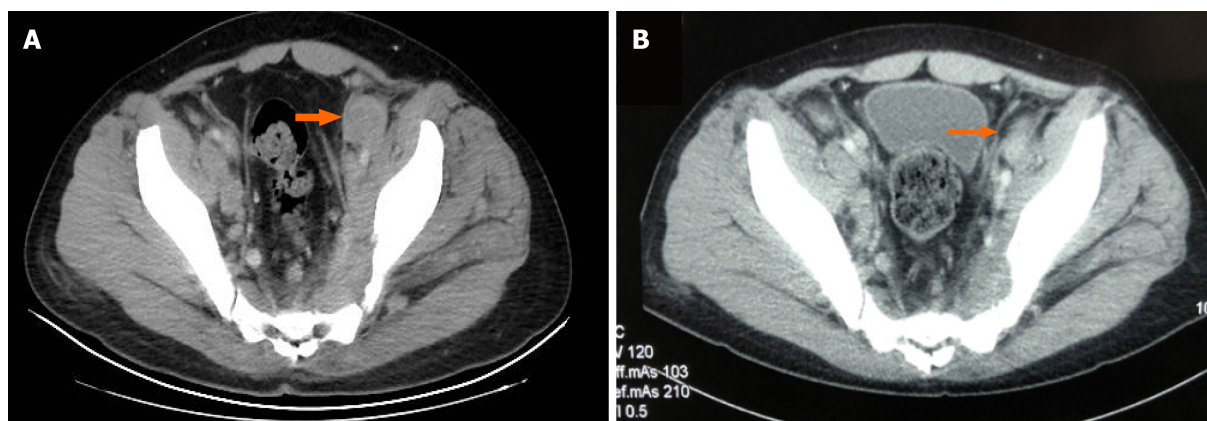


Figure 2 Computed tomography scan of the abdomen and pelvis before and after combination therapy. A: Imaging features before treatment; B: Imaging changes after three cycles of treatment.

free survival was 11.5 mo. The treatment was safe and well tolerated.

DISCUSSION

It is difficult to treat relapsed/refractory cHL patients with a heavy pretreatment history due to the lack of standard treatment options. PD-1 inhibitor is considered as a promising option. Programmed death-ligand 1 (PD-L1)/PD-L2 protein is often upregulated in Hodgkin lymphoma cells due to frequent copy-number gains of CD274 (PD-L1) and PDC1LG2 (PD-L2) on chromosome 9p24.1 and Epstein-Barr virus (EBV) infection, which binds the PD-1 receptor on T cells, inducing T-cell exhaustion through the inhibition of T-cell activation and proliferation[4]. In patients with relapsed/refractory cHL who experienced failure with both ASCT and BV, PD-1 blockade has an objective response rate of 65% to 87%[7,8]. However, most patients will ultimately experience progression with a median progression-free survival (PFS) of approximately 12 mo. Thus, an unmet medical need for effective therapies in patients who experienced failure with PD-1 blockade therapy remains.

Recently, a close association between epigenetic aberrations and immune escape has been explored in cHL. Ghoneim *et al*[9] reported that *de novo* DNA methylation programming is causal in reinforcing the development of T-cell exhaustion and establishes a stable cell-intrinsic barrier to PD-1 blockade, causing a decrease in the efficacy of anti-PD-1 antibodies, whereas methylation inhibition could enhance the antitumor activity of PD-1 blockade-mediated T-cell rejuvenation. Falchi *et al*[5] published their experience on a few patients with relapsed/refractory cHL, suggesting that treatment with a PD-1 inhibitor might result in higher complete remission rates as observed in 5/5 patients who were previously exposed to 5-azacitidine. A similar clinical conclusion was obtained by a single-center, two-arm, open-label phase II trial, which included 86 patients with relapsed/refractory cHL after failure of a median of four lines of therapy. In total, 25/86 had been previously exposed to PD-1 inhibitors, and nivolumab was the most commonly used drug, accounting for 72% of cases[6]. The PD-1 inhibitor used in this trial was camrelizumab, and the hypomethylating agent was decitabine, which has been approved to treat myelodysplastic syndromes and acute myeloid leukemia in the United States. The 25 patients with prior PD-1 inhibitor exposure were treated with a combination of 10 mg/d decitabine on days 1-5 and 200 mg camrelizumab on day 8 every 3 wk, and the objective response rate (ORR) and complete remission rate were 52% and 28%, respectively. The ORR was higher in patients with acquired resistance to PD-1 blockade compared to patients with primary resistance (62% *vs* 42%). At one year, the PFS and duration of response rates were 59% and 81%, respectively. Combination therapy could potentially reverse PD-1 resistance due to low-dose decitabine changing the epigenetic status of both tumors and immunocytes, increasing the infiltration of both CD8+ and CD4+ T cells, boosting T-cell function, enhancing tumor immunogenicity, and synergizing with anti-PD-1 antibodies to restore immunosurveillance[10-12]. Thus, hypomethylating agents might have a suppressive effect on tumoral immune escape in relapsed/refractory cHL. Another explanation for the reversal of PD-1 resistance may be attributed to the difference in the structure of different anti-PD-1 monoclonal antibodies. Anti-PD-1

Abs, including pembrolizumab, nivolumab, and other anti-PD-1s, all harbor wild-type Fc regions in the antibody structure. Binding to FcγR on macrophages compromises the antitumor activity of PD-1 monoclonal antibodies with the wild-type Fc region through activation of antibody-dependent macrophage-mediated killing of T effector cells [13,14]. Tislelizumab is a humanized IgG4 anti-PD-1 antibody specifically engineered to minimize binding to FcγR on macrophages. Preclinical data showed that in macrophage- and T cell-enriched conditions, tislelizumab did not induce antibody-dependent cellular phagocytosis; thus, its antitumor activity was not compromised [15].

Here, we report the case of a relapsed/refractory cHL patient who experienced failure with eight lines of therapy and was treated with a combination of low-dose decitabine plus tislelizumab and demonstrate that this combination approach is effective and safe. Further studies are needed to assess the therapeutic effect of this combination therapy in a larger cohort of patients with relapsed/refractory cHL.

CONCLUSION

The strategy of combining low-dose decitabine with tislelizumab could reverse the resistance to PD-1 inhibitors in patients with heavily pretreated relapsed/refractory cHL.

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