Advances in the treatment of Hodgkin's lymphoma (Review)

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Received December 16, 2022; Accepted March 22, 2023

DOI: 10.3892/ijo.2023.5509

Abstract. Hodgkin's lymphoma (HL) is a unique B-cell lymphoproliferative malignancy that has a critical pathogenesis characterized by a sparse population of Hodgkin and Reed-Sternberg cells surrounded by numerous dysfunctional immune cells. Although systemic chemotherapy with or without radiotherapy, has significantly improved the prognosis of the majority of patients with HL, a subset of patients remains refractory to first-line therapy or relapse after achieving an initial response. With the increased understanding of the biology and microenvironment of HL, novel strategies with notable efficacy and manageable toxicity, including targeted therapies, immunotherapy and cell therapy have emerged. The present review summarizes the progress made in developing novel therapies for HL and discusses future research directions in HL therapy.

Contents

1. Introduction

Hodgkin's lymphoma (HL) was first described in the year 1832 by Thomas Hodgkin, a British pathologist following the autopsies of 7 patients with lymphadenopathy and splenomegaly (1). Between the years 2014 and 2018, the prevalence of new HL cases was 26 individuals per million males and females. In addition, between 2015 and 2019, the annual mortality rate due to HL was 3 individuals per million males and females. Notably, the 5-year relative survival rate from 2011 to 2017 was 88.3% (data from Surveillance, Epidemiology and End Results, https://seer.cancer.gov/archive/csr/1975_2017/). It is estimated that HL accounts for ~10% of newly diagnosed lymphoma cases in the United States (8,480 of 85,720 cases), with a mortality rate of 4.6% (970 of 20,910 cases) (2).

Classical HL (cHL) is a highly curable malignancy treated with standard chemotherapy or chemoradiotherapy. However, there is significant percentage of patients, particularly those with advanced cHL, who will relapse or become refractory to initial therapy; however, the treatment options for relapsed or refractory (R/R) cHL are suboptimal (3-5). Salvage high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) in patients who are sensitive to chemotherapy has been the standard therapy for patients with R/R cHL and has been shown to achieve 50% curability (6-9). With an improved understanding of cHL biology and its tumor microenvironment, novel agents with marked efficacy have been developed, several of which have been approved by the US Food and Drug Administration (FDA) for patients with R/R cHL. Given the success of novel therapies for R/R cHL, these approaches have been explored or are being evaluated in other settings, including in combination with chemotherapy as frontline therapy, or consolidation following ASCT. Significant progress has been made in determining which patients benefit the most from these therapies and when to administer them. The present review summarizes the key clinical developments of novel therapies for HL and discusses the future directions in HL therapy (Fig. 1).

2. Anti-CD30 antibody-drug conjugate

Development of brentuximab vedotin (BV). The malignant cells in HL are comprised of Hodgkin and Reed-Sternberg (HRS) cells, which can be pathognomonic, multinucleate giant cells or large mononuclear cells (10). CD30, a member of the TNF receptor superfamily, is a surface antigen that is characteristically expressed on HRS cells. CD30 has a restricted expression in normal tissues, rendering it an ideal therapeutic target for cHL (11-14). Although several anti-CD30 antibodies, including anti-CD30 bispecific antibodies, anti-CD30 immunotoxins or anti-CD30 radiolabeled with iodine-131 have been evaluated in patients with R/R CD30-expressing lymphomas, the results have not been encouraging (15-20). BV is an antibody-drug conjugate (ADC) containing the potent antimitotic drug, monomethylauristatin E (MMAE), which is attached to the anti-CD30 monoclonal antibody, cAC10, through a cleavable dipeptide

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Key words: novel therapies, Hodgkin's lymphoma, brentuximab vedotin, immunotherapy, targeted therapy, cell therapy

linker. After the ADC is internalized through receptor-mediated endocytosis, the linker is exposed to proteolytic enzymes inside of the CD30-positive cells, followed by the release of MMAE. Intracellular concentrations of the released drug are high over a prolonged period of time; however, the amount of effluxed drug is also sufficient to exert bystander activity on surrounding CD30-negative cells (21).

BV plus chemotherapy as frontline therapy for advanced-stage HL. Although multi-agent chemotherapies, including the combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) can cure ~70-80% of patients with advanced-stage HL (4,22,23), the ABVD regimen is often associated with severe bleomycin-induced pulmonary toxicities which can be life-threatening (24-26). A phase I, a dose-escalation trial compared the efficacies of BV combined with ABVD or with doxorubicin, vinblastine and dacarbazine (AVD) as first-line therapy for treatment-naïve patients with advanced-stage HL. The complete remission (CR) rate was almost similar in the BV + ABVD and BV + AVD (95 vs. 96%) groups, although an unacceptable number of patients (44%) in the BV + ABVD group presented significant pulmonary toxicities, which was not experienced by any of the patients in the BV + AVD group (27). Long-term follow-up analysis revealed that the BV + AVD regimen had an estimated 5-year failure-free survival and overall survival (OS) of 92 and 100%, respectively (Table I) (28). Subsequently, a large randomized phase 3 study, ECHELON-1, reported a significant improvement in the 2-year modified progression-free survival (PFS) rates following treatment with BV + AVD as compared to ABVD (82.1 vs. 77.2%; P=0.04) for patients with stage III/IV cHL, and a decrease in the number of deaths that were not statistically significant from 28 deaths to 39 deaths (Table I) (29). According to the long-term follow-up results, the 3-year PFS rates in the BV + AVD and ABVD arms were 83.1 and 76.0%, respectively, where the BV + AVD regimen was favored by 7.1% (P=0.005) (30). Recent results have shown that the 5-year PFS rates in BV + AVD and ABVD groups were 82.2 and 75.3%, respectively (P=0.0017). Importantly, the BV + AVD group had fewer secondary malignancies than the ABVD group (31). Another study found that a combination of 1.8 mg/kg BV and 375 mg/m^2 dacarbazine for up to 12 cycles was active and well-tolerated in patients with treatment-naïve advanced HL aged >60 years, with an objective response rate (ORR) of 100% and a CR of 62%. The median PFS was 17.9 months at a median observation time of 21.6 months (32).

BV as monotherapy post-ASCT in cHL. For patients with R/R HL, salvage chemotherapy followed by ASCT has been the standard treatment with a cure rate of ~50% (7-9). A randomized, double-blind phase 3 trial, AETHERA, established BV as an effective consolidation therapy following ASCT in patients with cHL at high risk of relapse or progression. The median PFS by an independent review in the BV group (42.9 months) was superior to the placebo group (24.1 months), after patients received 16 cycles of 1.8 mg/kg BV or placebo intravenously every 3 weeks, starting 30-45 days following transplantation (33). Even at the 5-year follow-up, sustained PFS was found to favor the BV group. The 5-year PFS rates in the BV and placebo groups were 59 and 41%, respectively. Notably, patients with >2 risk factors with BV exhibited a significantly higher 5-year PFS than patients who received the placebo and patients who received BV as early consolidation delayed time to second subsequent therapy (34).

A pivotal phase II clinical trial demonstrated that the ORR and CR rates recorded for 102 patients with R/R HL after failed ASCT, who received a dose of 1.8 mg/kg BV every 3 weeks for up to 16 cycles, were 75 and 34%, respectively (35). At the 5-year follow-up, the estimated OS rate was 41% and the PFS rate was 22%. Among the 34 patients with CR, 6 patients who underwent a consolidative allogeneic stem cell transplantation following BV treatment had estimated 5-year PFS and OS rates of 67 and 83%, respectively, while the remaining 28 non-transplant patients with CR had estimated 5-year PFS and OS rates of 48 and 60%, respectively. The median OS and PFS were not attained in patients with CR (36). Based on these findings, BV appears to be an effective option not only as a consolidation therapy following ASCT, but also as a useful therapy after the failure of ASCT.

BV plus chemotherapy in R/R HL. In patients with R/R HL, BV has been evaluated in combination with traditional salvage chemotherapy. A phase II transplant BRaVE study was conducted to investigate the efficacy and safety of BV plus dexamethasone, cisplatin and cytarabine (DHAP) followed by high-dose chemotherapy (HDC) and autologous peripheral blood stem-cell transplantation (auto-PBSCT). According to the [18F] fluorodeoxyglucose-positron emission tomography (PET)-computed tomography (CT) results, 81% of the patients achieved metabolic CR (mCR) before HDC/auto-PBSCT, and 5 patients achieved metabolic partial remission and of which 4 converted to mCR after HDC/auto-PBSCT. The 2-year PFS and OS were 74 and 95%, respectively (37). A phase 2 trial that validated the improved curability following high-dose therapy (HDT)/ASCT treatment reported that of the patients with R/R HL who received the PET-based sequential salvage therapy with BV followed by augmented ifosamide, carboplatin and etoposide, 76% achieved a PET-negative status (38). The long-term results of a trial from the Spanish GELTAMO Group demonstrated that the combination of BV and ESHAP on R/R HL achieved ORR of 91%, including 70% CR prior to transplant. Following a subsequent ASCT, a CR of 82%, a PFS of 71%, and an OS of 91% was recorded at a median follow-up of 27 months (39).

The combination of BV and bendamustine has been confirmed as a highly potent salvage therapy leading to a high response prior to ASCT in patients with R/R HL. In a phase 1/2 trial, 55 patients with R/R HL received BV (1.8 mg/kg) on day 1 and bendamustine (90 mg/m^2) on days 1 and 2 every 3 weeks for up to six cycles followed by ASCT and/or BV monotherapy for up to 16 cycles. Following a median of two cycles of combination therapy, the ORR was 92.5%, with 73.6% of patients achieving CR (40). The OS at 3 years was 93% with no difference between patients who with ASCT or without ASCT; the PFS at 3 years was 60.3%, 67.1% for patients with ASCT and 40.4% without ASCT (41). Notably, a combination regimen of BV and bendamustine could safely achieve a high overall and complete response, serving as a potential and efficacious alternative to platinum-based chemotherapy before ASCT, even in heavily pre-treated patients with R/R HL (42). Of all patients who were administered a regimen consisting of 1.8 mg/kg BV

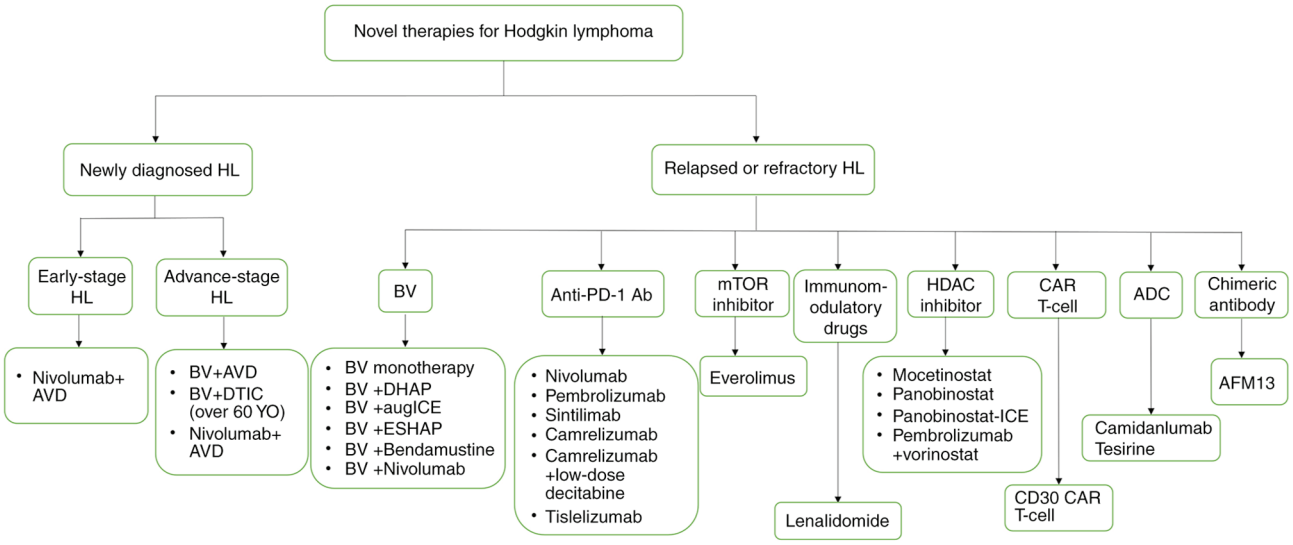

Figure 1. Therapeutic scheme for HL. HL, Hodgkin's lymphoma; AVD, doxorubicin, vinblastine and dacarbazine; BV, brentuximab vedotin; DTIC, brentuximab vedotin plus dacarbazine; augICE, augmented ifosamide, carboplatin, and etoposide; PD-1, programmed death 1; mTOR, mammalian target of rapamycin; HDAC, histone deacetylase; CAT T-cell, chimeric antigen receptor T-cell; ADC, antibody-drug conjugate.

on day 1 combined with 120 mg/m^2 bendamustine (bendamustine supercharge) per day on days 2 and 3 every 3 weeks for a total of four courses, 80% could accomplish a Deauville 5-point score of ≤2, which is an important indicator of favorable efficacy post-ASCT, and a 2-year PFS rate of 93.7%. Notably, bendamustine was increased to a higher dose and the timing of bendamustine was subsequently modified according to the preclinical theory that bendamustine administered after BV may exert a synergistic effect (43). Numerous clinical results from Italy have also shown the combination of BV and bendamustine to be a promising and effective salvage treatment with a manageable toxicity profile in patients with R/R HL (44,45). Given these noteworthy results, BV plus chemotherapy may be an efficacious therapy as a bridge to SCT for the improvement of curability in patients with R/R HL.

Safety and tolerance. Peripheral neuropathy is the most common toxicity associated with BV, accounting for 67% of toxicity cases, which often results in dose reduction and/or treatment discontinuation (34,36). When combined with systemic chemotherapy, including AVD, ESHAP or bendamustine, myelotoxicity with different grades, particularly neutropenia, frequently occurred (29,39,42). Granulocyte colony-stimulating factor primary prophylaxis may be effective for patients to reduce this toxicity (30,40). Of note, infusion-related reactions (IRRs) were reported in more than half of patients treated with BV and bendamustine and the majority of IRRs occurred during cycle two of combination therapy. Therefore, high-dose corticosteroid and antihistamine premedication were prophylactically prescribed with combination therapy; however, this approach only decreased the severity of IRRs and did not appreciably affect the incidence (40).

3. Immune checkpoint inhibitors

Programmed death 1 (PD-1) and its ligands, PD ligand 1 (PD-L1) and PD ligand 2 (PD-L2), exhibit inhibitory signals to regulate the balance between T-cell activation, tolerance and immunopathology. After the clearance of pathogens and tumors, PD-1 is required for the induction and maintenance of T-cell tolerance, where PD-L1 can limit effector T-cell responses and protect against immune-mediated tissue damage. Although T-cells can recognize the antigens present in tumors, the immunological clearance of tumors rarely occurs, which is partly due to immune suppression of the tumor microenvironment. The expression of PD-L1 on tumors contributes to this immunological suppression (46). The expression of PD-1 is markedly elevated in tumor-infiltrating T-cells of HL, while that of PD-L expression is upregulated on HRS cells (47). In cHL, chromosome 9p24.1 alterations have been shown to increase PD-L1 expression and further promote their induction via the copy number-dependent Janus kinase (JAK)2/signal transducer and activator of transcription (STAT) signaling pathway (48,49). Another mechanism of PD-L1 overexpression in cHL involves an Epstein-Barr virus infection (50). Due to these two mechanisms (9p24.1 amplification and Epstein-Barr virus infection), PD-1/PD-L1 blockade has been an ideal treatment for cHL.

Nivolumab. Nivolumab was the first anti-PD-1 antibody approved by the FDA for R/R cHL. In a heavily pre-treated population of patients with cHL, of whom 78% relapsed after ASCT and 78% relapsed after BV, all patients received 3 mg/kg nivolumab every 2 weeks. The ORR of nivolumab was 87%, with a CR of 17% and partial remission (PR) of 70%. Responses were durable, with 86% PFS at 6 months (51). Findings from the multicohort single-arm phase II trial, CheckMate 205, suggested that nivolumab may be associated with a favorable safety profile and long-term benefits across a wide range of patients with R/R cHL (Table II) (52). In that study, 243 patients were divided to three cohorts due to treatment history, including 63 patients in the BV-naïve (cohort A), 80 in the BV received after autologous hematopoietic cell transplantation (auto-HCT) (cohort B), and 100 in the BV

Table I. Clinical trials of brentuximab vedotin in Hodgkin's lymphoma.

Authors	Brentuximab vedotin	Study population	Sample size	Responses	Median progression-free survival	(Refs.)
Trials as monotherapy						
Moskowitz *et al*	Brentuximab vedotin	Patients with unfavorable risk, relapsed or primary refractory classic Hodgkin's lymphoma who had undergone autologous stem-cell transplantation	329	Not applicable	42.9 months; 5-year PFS of 59%	(33)
Younes *et al* Chen *et al*	Brentuximab vedotin	Patients with relapsed or refractory Hodgkin's lymphoma after autologousstem-cell transplantation	102	ORR 75%, CR 34%	5-year PFS of 22%	(35,36)
Trials in combination with chemotherapy						
Connors *et al*	Brentuximab vedotin plus AVD	Patients with previously untreated stage III or IV classic Hodgkin's lymphoma	664	ORR 86%, CR 73%	2-year modified PFS of 82.1%; 3-year PFS 83.1%	(29)
Friedberg *et al*	Brentuximab vedotin plus dacarbazine	Patients aged >60 years with treatment-naive Hodgkin's lymphoma	22	ORR 100%, CR 62%	17.9 months	(32)
Kersten *et al*	Brentuximab vedotin plus DHAP	Patients with primary refractory disease or a first relapse after first-line chemotherapy	55	ORR 90%, CR 81%	2-year PFS of 74%	(37)
Garcia-Sanz *et al*	Brentuximab vedotin plus ESHAP	Patients with relapsed/ refractory Hodgkin lymphoma after first-line chemotherapy	66	ORR 91%, CR 70%	30-months PFS of 71%	(39)
LaCasce *et al* LaCasce *et al*	Brentuximab vedotin plus bendamustine	Patients with relapsed or refractory disease following standard frontline chemotherapy	55	ORR 92.5%, CR 73.6%	2-year PFS of 62.6%; 3-year PFS of 60.3%	(40,41)
Picardi *et al*	Brentuximab vedotin plus bendamustine supercharge	Patients with relapsed or refractory classical Hodgkin's lymphoma after the failure of >1 salvage treatments	20	20 Patients with complete metabolic response	2-year PFS of 93.7%	(43)
Trials in combination with nivolumab						
Herrera *et al*	Brentuximab vedotin plus nivolumab	Patients with refractory or relapsed Hodgkin lymphoma	62	ORR 82%, CR 61%	6-months PFS of 89%	(56)

PFS, progression-free survival; AVD, doxorubicin, vinblastine and dacarbazine; DHAP, dexamethasone, high-dose cytarabine and cisplatin; ORR, objective response rate; CR, complete remission.

Table II. Clinical trials of anti-PD-1 antibody in Hodgkin's lymphoma.

Authors	Anti-PD-1 antibody	Study population	Sample size	Responses	Median progression-free survival	(Refs.)
Nivolumab						
Armand *et al*	Nivolumab	Patients with relapsed/efractory classical Hodgkin lymphoma after autologous hematopoietic cell transplantation failure	243	ORR 69%, CR 16%	14.7 months	(52)
Ramchandren *et al*	Nivolumab plus AVD	Patients with newly diagnosed advanced-stage classical Hodgkin lymphoma	51	ORR 84%, CR 67%	9-month modified PFS of 92%	(54)
Brockelmann *et al*	Nivolumab plus AVD	Patients with newly diagnosed early-stage unfavorable Hodgkin lymphoma	109	ORR 100% and CR 83% in concomitant group; ORR 98% and CR 84% in sequential group	12-month PFS of 100% for concomitant, and 98% for sequential	(55)
Herrera *et al*	Nivolumab plus brentuximab vedotin	Patients with refractory or relapsed Hodgkin lymphoma	62	ORR 82%, CR 61%	6-months PFS of 89%	(56)
Pembrolizumab						
Chen *et al*	Pembrolizumab	Patients with relapsed or refractory classic Hodgkin lymphoma	210	ORR 69%, CR 22.4%	13.6 months	(58)
Armand *et al*	Pembrolizumab	Patients with refractory or relapsed classical Hodgkin's lymphoma after autologous stem cell transplantation	30	ORR 100%	18-month PFS of 82%	(60)
Sintilimab						
Shi *et al*	Sintilimab	Patients with classical Hodgkin's lymphoma relapsed or refractory after two or more lines of therapy	96	ORR 80.4%, CR 34%	6-month PFS of 77.6%	(62)
Camrelizumab						
Song *et al* Nie *et al*	Camrelizumab	Patients with classical Hodgkin's lymphoma who had failed to achieve a remission or experienced progression after autologous stem	75	ORR 76%, CR 28%	12-month PFS of 66.5%	(66,67)

Table II. Continued.

Authors	Anti-PD-1 antibody	Study population	Sample size	Responses	Median progression-free survival	(Refs.)
Camrelizumab						
		cell transplantation or had received at least two lines of systemic chemotherapies				
Tislelizumab						
Song *et al* Song *et al*	Tislelizumab	Patients with relapsed or refractory classical Hodgkin's lymphoma after failure of ASCT or ineligible for ASCT	70	ORR 87.1%,	3-year PFS of 40.8%	(69,70)

PFS, progression-free survival; AVD, doxorubicin, vinblastine and dacarbazine; ASCT, autologous hematopoietic stem cell transplantation; ORR, objective response rate; CR, complete remission.

received before and/or after auto-HCT (cohort C). Following a median follow-up of 18 months, the ORR was 69% overall, including 16% of patients achieving CR and 53% achieving PR. The ORRs were 65, 68 and 73% in cohorts A, B and C, respectively, with CR in 29, 13 and 12% of patients, respectively. The median duration of response (DOR) and median PFS were 16.6 and 14.7 months, respectively, and the median OS was not reached. The response rates and median PFS were comparable in patients who received BV after or only before auto-HCT (52). In addition, the 5-year PFS and OS were 18 and 71%, respectively. It appears feasible to terminate the use of nivolumab after 1 year of CR and restart therapy upon disease progression (53). Subsequently, the results from cohort D of the CheckMate 205 trial revealed that nivolumab monotherapy followed by nivolumab plus doxorubicin, vinblastine and dacarbazine (N-AVD) was a safe and efficacious regimen for newly diagnosed, advanced-stage cHL. The cohort had a total of 51 patients who received 4 doses of nivolumab monotherapy, followed by 12 doses of N-AVD; doses administered every 2 weeks, and nivolumab (240 mg) was administered intravenously. The ORR was 84%, with 67% CR and a 9-month modified PFS of 92%. Patients with a higher PD-L1 expression on HRS cells tended to have more favorable responses to nivolumab monotherapy (P=0.096), and significantly deeper and more durable responses to N-AVD (P=0.041) (54). Recently, nivolumab and AVD was evaluated for patients with early-stage unfavorable HL in a randomized phase 2 German Hodgkin Study Group NIVAHL trial (55). A total of 109 patients were randomly assigned (1:1) to receive either a concomitant treatment with four cycles of N-AVD or sequential treatment with four doses of nivolumab, two cycles of N-AVD, and two cycles of AVD. For both groups, a consolidating 30-Gy involved-site radiotherapy (IS-RT) was scheduled post-systemic treatment. At interim evaluation after two cycles of N-AVD or four doses of nivolumab monotherapy, the ORR was 100 and 96%, with CR in 87 and 51%, respectively. Following treatment, the CR was 90 and 94% in the concomitant treatment and sequential treatment, with a 12-month PFS of 100 and 98%, respectively (55).

In addition to the high response rates achieved with nivolumab and BV monotherapies, their combination has also been reported to be well-tolerated and highly effective as a first salvage therapy in patients with R/R HL. An ORR of 82% and a CR of 61% were recorded for the combination, which was higher than BV or nivolumab monotherapy in R/R HL. Importantly, the responses were achieved in an outpatient setting, where nausea, fatigue and infusion-related reactions were the most common adverse events (AEs) and differed from toxicities associated with traditional salvage chemotherapy (56). Based on these clinical trial results, nivolumab not only exhibits impressive responses in R/R HL, but also exhibits notable efficacy in addition to AVD in newly diagnosed patients.

In comparison to pembrolizumab, nivolumab (3 mg/kg, every 2 weeks) had higher mean incidences of all-grade AEs and AEs of grade ≥3 (57). When nivolumab was administered as monotherapy, the most common drug-related AEs of any grade were fatigue, diarrhea and IRRs and most common grade 3 or 4 drug-related AEs were elevated lipase, neutropenia and elevated levels of alanine aminotransferase (ALT). A few patients discontinued treatment primarily due to pneumonitis and autoimmune hepatitis (52). When combined with multi-agent chemotherapy, such as AVD, hematologic AEs of grade ≥3 most commonly occurred, which warrants caution particularly in patients over the age of 60 (54,55). In another combination regimen of BV and nivolumab, a relatively

higher proportion of patients (44%) experienced IRRs mostly during cycle 2 of the study therapy, most of which were grade 1 or 2 (56).

Pembrolizumab. Pembrolizumab is a fully humanized IgG4/κ anti-PD-1 monoclonal antibody. A large phase II trial, KEYNOTE-087, which enrolled 210 patients with R/R cHL, demonstrated that 69 patients relapsed after ASCT followed by BV (cohort 1), 81 patients relapsed after salvage chemotherapy and BV without ASCT (cohort 2) and 60 patients relapsed after ASCT without BV (cohort 3). All patients received pembrolizumab 200 mg once every 3 weeks without premedication for a maximum of 24 months. According to the blinded independent central review, the ORR and CR were 69.0 and 22.4%, respectively. In cohorts 1, 2 and 3, the ORRs were 73.9, 64.2 and 70.0%, respectively, while the CRs were 21.7, 24.7 and 20.0%, respectively (58). With a median of 39.5 months of follow-up, pembrolizumab continued to exhibit efficacious and durable antitumor activity in patients with R/R cHL, as the ORR was 71% with a 27.6% CR and a 43.3% PR. The overall median PFS was 13.6 months, and the PFS of cohorts 1, 2 and 3 were 16.4, 11.1 and 19.4 months, respectively. The median OS was not reached in the total population or any cohort. Notably, 17 patients received an additional 17 cycles of pembrolizumab (second-course) as they experienced disease progression upon discontinuing pembrolizumab after achieving an initial confirmed CR post-6 months of treatment. The second-course treatment could re-induce remission in most patients who previously reached CR, including 31.3% of patients in CR and 37.5% of patients in PR (59). Additionally, pembrolizumab has been demonstrated as effective with an acceptable safety profile in patients with R/R cHL after ASCT. The PFS at 18 months was 82% and OS was 100% (60). The most common treatment-related AEs (TRAEs) were hypothyroidism and pyrexia. And the most common grade 3 or 4 TRAEs were neutropenia, dyspnea and diarrhea (58). For transplant eligible R/R cHL patients, pembrolizumab plus gemcitabine, vinorelbine and liposomal doxorubicin (pembro-GVD) as second-line therapy achieved 100% of patients with ORR and 95% with CR in a phase II study. Among the 38 evaluable patients, 36 (95%) patients received HDT/AHCT and all transplanted patients were in remission at a median post-transplant follow-up of 13.5 months. The majority of AEs were grade 1 or 2, and few grade 3 AEs included rash (n=1), elevated AST/ALT (n=4), mucositis (n=2), neutropenia (n=4) and hyperthyroidism (n=1) (61).

Sintilimab. Sintilimab, a highly selective and fully humanized anti-PD-1 monoclonal antibody, was evaluated in a phase II trial, ORIENT-1, which involved 96 adult patients from 18 hospitals in China with R/R cHL who had received two or more lines of therapy (62). All the patients received sintilimab at 200 mg administered intravenously over a period of 30-60 min, once every 3 weeks. In the full analysis set (n=92), the ORR and CR were 80.4 and 34%, respectively, with 18% of patients exhibiting mCR according to PET-CT scans, and 27% exhibiting CR on contrast-enhanced CT scans. The PFS at 6 months was 77.6% by the cut-off date, and the median PFS was not attained. All patients experienced at least one treatment-emergent AE, the majority of which were grade 1 or 2, and 25% of patients had grade 3 or 4 AEs. The most common TRAE was pyrexia (41%), and the drug-related severe AEs were pneumonitis (3%), lung infection (3%) and infusion reaction (2%) (62).

Camrelizumab. Camrelizumab (SHR-1210) is a humanized high-affinity IgG4 anti-PD-1 monoclonal antibody that has exhibited promising antitumor efficacies with manageable toxicities in clinical trials (63-65). In a phase II study, 75 patients who had failed to achieve remission status, experienced progression following ASCT or had received at least 2 prior lines of systemic chemotherapies were administered camrelizumab at 200 mg every 2 weeks. With a median follow-up of 12.9 months, the ORR was 76%, with a CR and PR of 28 and 48%, respectively. According to the independent review committee assessment, the 12-month PFS rate was 66.5% and the median OS was not reached (66). Notably, low-dose decitabine, a hypomethylating agent, in addition to camrelizumab can lead to a significantly higher CR rate than camrelizumab alone in patients with R/R cHL. Even for patients who relapsed or were refractory to prior anti-PD-1 monotherapy such as nivolumab and pembrolizumab, there were still 52% of patients who benefited from the combination of decitabine and camrelizumab, with 28% achieving CR (67). It is worth noting that the most common treatment-related AE was cutaneous reactive capillary endothelial proliferation with all grade 1 or grade 2, both in monotherapy group (84%) or combined with decitabine (87%). The pathological results from a few patients indicated the benign proliferation of endothelial cells in the lesion tissue (66,67).

Tislelizumab. It has been reported that FcϒR receptor compromises the antitumor activity of anti-PD-1 antibodies as the activity of anti-PD-1 antibodies are FcϒR receptor-independent (68). Tislelizumab is an investigational humanized IgG4 monoclonal antibody binding to the extracellular domain of human PD-1 with high specificity and affinity. In addition, tislelizumab was specifically engineered to minimize FcϒR receptor binding on macrophages, which may abrogate antibody-dependent phagocytosis. In a multicenter, single-arm, phase 2 study, 70 patients with R/R cHL after the failure of or ineligible of ASCT were enrolled and treated with tislelizumab at 200 mg intravenously every 3 weeks. With a median follow-up of 33.8 months, the ORR was 87.1% and CR was 67.1%. The 3-year OS and PFS rates were 84.8 and 40.8%, respectively. While 97.1% of patients experienced treatment-emergent AEs (TEAEs) of any grade, 41.4% experienced grade ≥3 TEAEs. The most common TEAEs were pyrexia (57.1%), upper respiratory tract infection (38.6%), hypothyroidism (37.1%), weight gain (34.3%), cough (21.4%), a decrease in white blood cell count (21.4%) and an increase in ALT levels (20.0%). TEAEs leading to treatment discontinuation occurred in 6 (8.6%) patients, including pneumonitis in two patients, and focal segmental glomerulosclerosis, organizing pneumonia, psychomotor skills impaired and seizure in one patient. Correlative biomarker analysis identified that FcϒR receptor I-expressing macrophages had no observed impact on either the CR or PFS rate achieved with tislelizumab. Patients with a shorter PFS were associated with 'B-cell marker' cluster including *CD19*, *CD22*, *CD72* and *CD79B* genes, along

with interferon regulatory factors, including *IRF1*, *IRF2*, *IRF3*, *IRF8* and *IRF9* (69,70).

SEA-TGT. T-cell immunoglobulin and ITIM domain (TIGIT) is an inhibitory receptor exclusively expressed on lymphocytes including cytotoxic T-cells, helper T-cells, regulatory T-cells and natural killer (NK) cells. The primary ligand of TIGHT is CD155, which is expressed in healthy tissues including monocytes, dendritic cells and endothelial cells, as well as in cancer cells (71-73). Based on these insights, TIGIT may be a potential target for patients with HL. A phase I, multicenter, dose-escalation/expansion study, SCNTGT-001, is currently underway to investigate the safety and preliminary efficacy of SEA-TGT, an effector-function enhanced human monoclonal antibody targeting TIGIT, in multiple relapsed, refractory or progressive metastatic solid tumors including cHL (74).

4. Other targeted and cell therapies

Ruxolitinib. It has been demonstrated that the JAK-mediated signaling pathway is upregulated in several patients with HL (75), and its blockade can inhibit HL cell proliferation. In addition, the genomic amplification of 9p24.1, which includes the JAK2 locus, is commonly observed in HL and results in the activation of STAT6 that stimulates tumor cell growth (76,77). Ruxolitinib is the first potent and selective inhibitor of JAK1/2 that can be administered orally. In a phase II study on 32 evaluable patients with R/R HL, ruxolitinib (15 or 20 mg) was administered twice daily. Following six cycles, the ORR was 9.4%, with the optimal ORR being 18.8%. The median DOR, median PFS and median OS were 7.7, 3.5 and 27.1 months, respectively. A total of 40 AEs were observed in 14/33 patients (42.4%) and 25 of which were grade ≥3. All AEs were considered to be related to ruxolitinib, with anemia being the most common. Other main causes of AEs of grade ≥3 included lymphopenia and infections (78). Another clinical study, involving 13 patients with R/R HL who received ruxolitinib at 20 mg twice daily every 28 days, reported that the disease control rate was 54%, including 1 patient with CR, 5 patients with PR and 1 patient with stable disease (SD). JAK2 amplification via FISH analysis was shown in 4 patients with HL with PR or SD. The median PFS was 3.6 months and the median OS was not reached within the median follow-up of 37.0 months. Treatment-related AEs were reported in 14 patients (73.6%), although the majority of events were mild (grade 1 or 2) (79). Based on these results, ruxolitinib exhibits a long-term clinical activity with mild toxicity, which may be combined with other regimens in the future.

Everolimus. Preclinical evidence has indicated that phosphatidyl-inositide 3 kinase (PI3K) and its substrate Akt are constitutively activated in HL-derived cell lines. Moreover, several downstream effectors of Akt signaling, including glycogen synthase kinase 3 and mammalian target of rapamycin (mTOR) substrates 4E-BP1 and p70 S6 kinase, have also been found to be phosphorylated in HL cells (80). Everolimus, an oral mTOR inhibitor, has been confirmed to exert an antitumor effect in HL cells (81). A phase II clinical trial reported that 10 mg everolimus daily was administered to 57 patients that had relapsed following HDT/ASCT and/or a gemcitabine-, vinorelbine- or vinblastine-containing regimen. The ORR was 45.6%, including 8.8% of patients in CR and 36.8% of patients in PR. The median PFS was 8.0 months, with 12% of patients having a response duration >1 year. The most common TRAEs were thrombocytopenia, fatigue, anemia, rash and stomatitis (82). Another phase I/II multicenter trial conducted by the German Hodgkin Study Group evaluated the effect of adding everolimus to the standard DHAP towards improving the CR rate of reinduction chemotherapy. Although the addition of everolimus to DHAP was feasible, the efficacy of the combinatorial therapy failed to achieve an improvement (83).

Lenalidomide. Lenalidomide, a thalidomide analogue, exhibits multiple mechanisms of action, including the direct induction of apoptosis in malignant cells, antiangiogenic effects and indirectly affects the tumor microenvironment, such as the activation of NK cells and T-cells (84-86). It has been long recognized that the critical cHL pathogenesis is scant HRS cells surrounded by the tumor microenvironment. In a phase II trial, 38 heavily pre-treated patients were administered lenalidomide at 25 mg daily on days 1-21 of a 28-day cycle until the occurrence of an unacceptable AE or disease progression. Among these patients, 33 patients had received a stem cell transplantation and had a median number of four prior therapies. The results revealed an ORR of 19%, a cytostatic ORR of 33%, a median PFS of 4 months, and a median OS of 20 months. The treatment was well-tolerated, with hematological toxicities being the most common grade 3 or 4 AE (87). Another phase I study that enrolled patients aged ≥60 years with early unfavorable- or advanced-stage HL who received 4-8 cycles of AVD and lenalidomide in escalation with overdose control confirmed ORRs of 67 and 94% with a lenalidomide dose of 20 and 25 mg, respectively. Although the results demonstrated that this combination was highly effective and feasible, with the 3-year estimates for PFS and OS being 69.7 and 83.8%, it caused severe hematological acute toxicities, suggesting that this may not be an ideal regimen in older patients with HL (88). Since both everolimus and lenalidomide have exhibited clinical efficacies as single agents in patients with R/R HL and non-HL, a phase I/II trial attempted to evaluate the activity this combination at the Mayo Clinic. The ORR in the cHL cohort of 10 patients was 25%, with 2 patients each obtaining CR and PR, respectively (89).

Histone deacetylase (HDAC) inhibitors. HDACs are involved in multiple important cell functions, including cell cycle progression, angiogenesis, cell differentiation and apoptosis, and immunity. Therefore, HDAC inhibitors can be used as an antitumor therapy against a broad spectrum of hematologic and solid neoplasms (90,91). Mocetinostat, an oral isotype-selective HDAC inhibitor, was evaluated in R/R HL with two different dose cohorts (85 and 110 mg). A total of 51 patients received mocetinostat three times weekly for every 28 days a cycle. Of these, 81% of patients who completed at least two cycles of therapy exhibited a reduction in tumor measurements, and the ORRs were 35 and 21% for the 110 and 85 mg dose cohorts, respectively. There were 4 patients that succumbed during the study, all in the 110 mg cohort, with two of these deaths considered to be treatment-related. Mocetinostat, at a dose of

85 mg, demonstrated improved tolerance without a reduced efficacy and should be used for developing a single agent in the future (92). Panobinostat, a potent pan-deacetylase inhibitor, was administered at 40 mg orally three times a week in 129 patients with heavily pre-treated cHL. A total of 96 patients (74%) had tumor reductions with an ORR of 27%, a CR of 4% and a PR of 23%. However, not all patients responded to the immediately preceding panobinostat and the median time to response was 2.3 months. In addition, the DOR was 6.9 months and the median PFS was 6.1 months. Gastrointestinal AEs were generally grade 1 and 2 and most common grade 3 and 4 toxicities were manageable hematological AEs, primarily thrombocytopenia (93). The results from a phase 2 study that evaluated the efficacy of vorinostat in R/R HL were not encouraging, with an ORR of 4% and a median PFS of 4.8 months (94). The preliminary results from a phase I trial of pembrolizumab plus vorinostat in patients with R/R HL revealed that the combination produced objective responses with an ORR and a CR of 100 and 44%, including patients who had a disease progression before an anti-PD1 treatment (95).

Several studies have demonstrated that HDAC inhibitors can synergize the antitumor effects of chemotherapeutic agents in HL cell lines (96-98). A small number of patients with R/R cHL were recruited to evaluate the efficacy and safety of panobinostat in combination with ifosfamide, carboplatin, etoposide (P-ICE) in a phase I/phase II study. The results revealed that P-ICE exhibited an excellent response, with a CR of 82% in the P-ICE arm compared with 67% in the ICE arm, but with increased myelosuppression (99). Another combination of panobinostat and lenalidomide in patients with R/R HL was evaluated in a phase I/II trial. However, the recorded efficacy was limited with an ORR of 16.7% and a median PFS of 3.8 months, and severe AEs, such as neutropenia and febrile neutropenia, indicating that further evaluation was not warranted (100).

Camidanlumab tesirine. The antibody-drug conjugate, ADCT-301 (camidanlumab tesirine), is composed of an anti-CD25 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin. As CD25 is expressed on the cell surface of a number of lymphoma types, including cHL, a phase I clinical trial was conducted to evaluate the efficacy of camidanlumab tesirine in patients with R/R cHL (101). The study enrolled 60 patients with the median number of prior therapies being five (range, 2-15). The ORR and CR in 55 patients were 69.1 and 43.6%, respectively. The recommended dose of camidanlumab tesirine was 45 μg/kg every 3 weeks with an ORR of 80.8% and a CR of 50%. The ORR was 80.8% for patients who had previously received BV and 80.0% for those who had received both checkpoint inhibitors and BV. The ORR was 85.7% for those who received a checkpoint inhibitor, BV and a hematopoietic cell transplant. The median PFS and DOR were 6.7 and 7.7 months, respectively. The most common grade 3 and 4 TEAEs were liver dysfunction (36.7%), maculopapular rash (13.3%), anemia (8.3%) and thrombocytopenia (5.0%) (101).

AFM13. AFM13 is the first bispecific and tetravalent chimeric antibody that can specifically recruit NK cells by binding to CD16A and targeting CD30 expressed on tumor cells. In a phase 1 clinical study, AFM13 was administered to 28 patients with heavily pre-treated R/R HL with doses ranging from 0.01 to 7 mg/kg, where doses >1.5 mg/kg exhibited more potent efficacy (102). The maximum tolerated dose was not reached. The overall disease control was 61.5%, achieving a PR of 11.5% and a SD of 50%. Of the 7 patients who had received BV as the most recent therapy, 6 patients had SD after AFM13 treatment. Of note, the majority of AEs were mild to moderate, including fever (53.6%), chills (39.3%), headache (28.6%), nausea (17.9%), nasopharyngitis (17.9%), infusion reaction (14.3%), rash (14.3%), vomiting (14.3%) and pneumonia (14.3%) (102).

The combination of AFM13 and pembrolizumab is currently being evaluated as a potent and well-tolerated salvage regimen in patients with R/R HL. A phase 1b clinical trial enrolled 30 patients with R/R HL who had a median age of 34 years and a median number of prior therapies of four. All patients had previously failed standard treatments including BV, while 13 had BV as their most recent therapy. In the 23 patients with maximum administered dose, the ORR and CR were 87 and 35%, respectively. The most common AEs were IRRs (80%), rash (30%), pyrexia (23%), nausea (23%), diarrhea (20%), fatigue (17%), headache (17%) and elevated aspartate aminotransferase (13%), and elevated alanine aminotransferase (10%); however, the majority of IRRs were manageable without treatment discontinuations (103).

Chimeric antigen receptor (CAR) T-cell therapy. CAR T-cell therapy for hematological malignancies has been a breakthrough advancement in recent years. CARs are recombinant antigen receptors that contain an antigen recognition domain and a T-cell signaling domains (104-106). Therefore, CD30 CAR T-cell therapy is another method which can be used to specifically target the surface antigen CD30 of HL, apart from BV. In a phase I clinical trial, 18 patients with heavily pre-treated R/R cHL were infused with a mean of $1.56x10^7$ (range, 1.1-2.1) CAR T-cells/kg after conditioning regimens. The PFS was 6 months and 7 patients achieved PR with 6 patients with SD (Table III). The CD30 CAR T-cell infusion was safe and tolerable. The most common treatment-related AEs included nausea/vomiting (27.8%) and urticarial-like rash (11.1%) (107). When compared to the results from the study by Wang *et al* (107), which used lymphodepletion before CAR T-cell infusion based on the more general practice, that study demonstrated the direct effects of CD30 CAR T-cells as a major strength. The optimal responses observed mainly occurred in patients with low soluble CD30, since CD30 is present in a soluble form in the plasma of HL patients with advanced/aggressive disease (108), suggesting that the affinity of the single-chain variable fragment (scFv) and a lower burden of disease may be important. Additionally, that study proposed that CD30 CAR T-cells may synergize PD1/PD-L1 blockade (109).

Another study evaluated the efficacy and safety of CD30 CAR T-cell therapy in 9 patients with R/R $CD30^+$ lymphoma (110). The study enrolled 6 patients with HL and 3 patients with anaplastic large cell lymphoma who were administered a median dose of $1.4x10^7$/kg CD30 CAR T-cells. The results were promising, with 7 patients achieving CR at the first visit and a median PFS of 13 months. Moreover, 3 patients with CR continued to be in remission for >2 years. A total of 5 patients with HL, refractory to anti-PD-1 antibody

Table III. Clinical trials of CAR T-cell therapy in Hodgkin's lymphoma.

Authors	Study population	Sample size	CAR T-cell dose	Responses	Median progression-free survival	(Refs.)
CD30 CAR T-cell therapy						
Wang *et al*	Patients heavily pre-treatedwith R/R cHL	18	$1.56x10^7$ (range, 1.1-2.1)	7 Patients in PR, and 6 patients in SD	6 months	(107)
Ramos *et al*	Patients with R/R HL or anaplastic large cell lymphoma	9	Three doses, $2x10^7$, $1x10^8$, $2x10^8$	3 Patients in CR, 3 patients with SD	Not reported	(109)
Wang *et al*	Patients with R/R $CD30^+$ lymphoma, including 6 HL and 3 anaplastic large cell lymphomas	9	Median dose of $1.4x10^7$/kg (range, 0.7-3.2)	7 Patients in CR at the first visit; 4 patients in relapse after 10 weeks; 3 patients with CR for over 2 years	13 months	(110)
Ramos *et al*	Patients with heavily pretreated R/R HL	41	From $1x10^8/m^2$ to $2x10^8/m^2$	ORR 62%, CR 51%	1-year PFS 36%	(111)
CART19 therapy						
Svoboda *et al*	Patients heavily pre-treated with cHL	5	From $7.46x10^5$/kg to $2.11x10^6$/kg	1 Patient with CR, 1 in PR, 1 with SD, 1 with PD and 1 categorized as not applicable	Not reported	(114)

CAR T-cell, chimeric antigen receptor T-cell; CART19, anti-CD19-directed CAR-modified T-cells; R/R, relapsed or refractory; HL, Hodgkin's lymphoma; cHL, classical Hodgkin's lymphoma; SD, stable disease; CR, complete remission; ORR, objective response rate; PD, progressive disease.

treatment were infused with anti-PD-1 antibody again; one relapsed patient regained a CR status and the other 4 patients sustained CR for at least a further 8 months, which indicated a synergistic effect of CD30 CAR T-cell therapy with the subsequent anti-PD-1 antibody treatment. Most AEs were mild, and it was reported that patients with a greater tumor burden may exhibit a more severe cytokine release syndrome (CRS) (110).

In a phase I/II clinical trial, 41 patients with heavily treated R/R HL received autologous CD30 CAR T-cell therapy. The median number of prior therapies was 7, including BV, immune checkpoint inhibitor and stem cell transplantation. The dose levels of CD30 CAR T-cells ranged from $1x10^8/m^2$ to $2x10^8/m^2$. Although 10 patients (24%) developed CRS, all reported events were grade 1 and all patients recovered without tocilizumab and/or steroids. Some patients experienced prolonged cytopenias, particularly thrombocytopenia without significant complications. The ORR was 62% and the CR was 51%. The 1-year OS and 1-year PFS were 94 and 36%, respectively. Notably, CD30 CAR T-cells at the dose of $2x10^8/m^2$ after fludarabine-based lymphodepletion exhibited notable efficacy with no significant toxicity (111).

A pilot study reported the results of 5 patients undergoing the successful manufacturing of non-viral RNA anti-CD19-directed CAR-modified T-cells (CART19), on the hypothesis that some circulating $CD19^+$ B cells are putative HRS stem cells (112) and cytokines produced by CART19 potentially changing the tumor microenvironment (113). This non-viral RNA CART19 was manufactured by transfecting T-cells with messenger RNA using electroporation, resulting in transient expression of CAR, which limited the potential for AEs. There were no severe toxicities with transient response (114).

5. Conclusions and future perspectives

Advances in HL treatment have significantly improved patient survival. While radiotherapy and chemotherapy have been the primary regimens for HL for decades, HSCT is considered a salvage therapy for R/R HL (115), although it is associated with high relapse rates (40%) (116). With a

better understanding of HL and its associated tumor microenvironment, the antibody-drug conjugate, BV and immune checkpoint inhibitors have exhibited marked antitumor efficacies in R/R cHL. A combination of anti-PD-1 antibodies and BV may be an effective treatment option for patients who are untreated, localized and intolerant to chemotherapy. For patients who are untreated with advanced-stage HL and are eligible to receive anti-PD-1 antibodies, AVD combined with anti-PD-1 antibody for six cycles may be effective. Patients can also receive a combination of AVD and BV therapy to avoid the toxicity of bleomycin. Patients experiencing a first relapse are encouraged to receive salvage chemotherapy followed by ASCT. In addition, administering anti-PD-1 antibodies may be a therapeutic option for refractory patients, while BV may be used in patients who are contradictory to anti-PD-1 antibodies. Patients who have failed both anti-PD-1 antibody and BV, can choose from other targeted therapies including lenalidomide, PI3K/mTOR inhibitors, HDAC inhibitor, CD25 antibody-drug conjugate or anti-CD30 CAR T-cell therapy. The integration of these novel strategies into early lines of therapy may prove beneficial to achieve higher curability, sustained benefits and manageable toxicity. In addition to these therapies, other agents with various mechanisms also demonstrate a certain level of efficacy. Notably, CD30 CAR T-cell therapy exhibits potent clinical activity in R/R HL and is well-tolerable with manageable toxicity. However, further studies are required to focus on developing a personalized regimen for each patient, in order to make it easier to select the optimal treatment with appropriate timing and minimal the long-term toxicity.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

YC and XS conceived and designed the study. YC wrote the manuscript. XD, LX, JZ, XZ, NL and XS revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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