Available online at www.sciencedirect.com

ScienceDirect

Chronic Diseases and Translational Medicine 5 (2019) 15−24

www.keaipublishing.com/en/journals/cdtm/

www.cdatm.org

Perspective

Current advances in Hodgkin's lymphoma

Joseph Vadakara*, Benjamin Andrick

Department of Hematology and Oncology, Geisinger Medical Center, Danville, PA 17822, USA

Received 21 August 2018

Available online 19 March 2019

Abstract

Hodgkin's lymphoma is a highly treatable malignancy. It has high cure rates yet there are many patients who relapse or are refractory to treatment. Traditionally, treatment has been with conventional chemotherapy; however, the development of brentuximab vedotin and immune checkpoint inhibitors has revolutionized the care of Hodgkin's lymphoma. This is a review of the current advances in the management of Hodgkin's lymphoma and a review of ongoing clinical trials in the field.

© 2019 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Hodgkin's lymphoma; Brentuximab vedotin; Nivolumab; Pembrolizumab; Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)

Introduction

Hodgkin's disease (HD) is a relatively uncommon B cell lymphoid malignancy. It has a bimodal age distribution with a peak incidence in the 15−34-year age group and a second in the over 60-year-old group in which the incidence is about 6 cases per 100,000 population per year. In Asia, however, there is no bimodal incidence and HD is most common among older patients with incidence rates half of those in Europe.[1] Treatment options for HD have evolved over time ranging from radiation, cytotoxic chemotherapy, cellular therapies and most recently targeted therapies. This article reviews some of the current advances in the treatment of Hodgkin's lymphoma.

Historical background

HD was first described by Hodgkin in 1832 where he described the autopsy findings of seven patients with HD.[2]

Radiation therapy, which was initially used for palliation and later with curative intent, was the first modality to be used in the treatment of HD. As techniques for radiation therapy improved, so did survival. While rarely used today, mantle field radiation was first used in the 1960s to boost cure rates. It involved radiation to the neck, chest, and axillae to cover all the main lymph nodes in the upper half of the body. Later, with improved techniques and the evolution of combined modality treatments, there was a move toward involved field radiation therapy (IFRT) and involved site radiation therapy (ISRT).[3,4]

* Corresponding author. 100 N Academy Avenue, Danville, PA 17822, USA. Fax: +1 5702716542.

E-mail address: joseph.vadakara@gmail.com (J. Vadakara).

Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.cdtm.2019.02.003

2095-882X/© 2019 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The first effective use of chemotherapy in HD was with nitrogen mustard when Goodman et al[5] treated 27 patients with nitrogen mustard, many of these patients were thought to have disease resistant to radiation. Several patients had a significant reduction in tumor burden and improvement in symptoms lasting several weeks to months. This response, though impressive, was not durable. Further improvements in the management of HD came with the introduction of vinca alkaloids like vinblastine.[6]

Building upon the efficacy of monotherapies, combination therapy emerged in the form of nitrogen mustard, vincristine, procarbazine and prednisone (MOPP) which further improved survival rates.[7] The most significant and long-lasting breakthrough came with the introduction of bleomycin and its incorporation into the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen. This regimen improved upon the MOPP regimen and became a standard worldwide, particularly in the United States, for several decades.[8]

Efforts to improve on the efficacy of the ABVD regimen by the German Hodgkin Study Group (GHSG) included the cyclophosphamide, vincristine, procarbazine, and prednisone alternating with ABVD (COPP-ABVD) regimen, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) and increased-dose BEACOPP.[9] Previous studies had shown that ABVD and BEACOPP had a similar efficacy with more acute and long-term toxicities associated with the later.[10,11] However, emerging data have shown that the BEACOPP and escalated BEACOPP (BEACOPPesc) regimens improve both overall survival (OS) and progression-free survival (PFS) for patients with early unfavorable and advanced HD.[11–14] Thus, BEACOPP is a widely utilized regimen, particularly in Europe.

The effort to mitigate cardiotoxicity and pulmonary toxicity due to anthracyclines and bleomycin exposure led to the development of the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone) with or without radiation.[15] The Stanford V regimen decreased the cumulative doses of anthracyclines and bleomycin. Studies comparing Stanford V to ABVD did not show significant differences in response rates or survival.[16,17] Thus, in North America ABVD remains a cornerstone of treatment for HD.

The recent development of the antibody drug conjugate brentuximab vedotin (BV) revolutionized the management of HD.[18] Brentuximab is a chimeric anti-CD30 antibody SGN-30 conjugated to the antitubulin monomethyl auristatin E (MMAE). While brentuximab was initially approved for relapsed disease, it subsequently garnered indications for post-autologous transplant maintenance therapy, and most recently, as first-line treatment in HD.[18]

The discovery that HD is associated with 9p24.1 amplification and increased programmed death-ligand 1 (PD-L1), and programmed death-ligand 2 (PD-L2) expression led to clinical trials of immune checkpoint inhibitors for this disease. Ultimately, such investigations led to the approval of nivolumab, an anti-programmed death-1 (PD-1) antibody, in the relapsed setting.[19] Clinical trials are ongoing to identify the role of checkpoint inhibitors in the treatment of earlier phases of the disease.

Furthermore, the understanding that HD is often associated with Epstein-Barr virus (EBV) has led to cellular therapies using EBV specific cytotoxic T cells. With the development of chimeric antigen receptor T-cell (CART) therapy, treatment for HD has advanced further.

Frontline therapy for HD

Initial treatment of HD has remained the same over the past several decades and has involved use of ABVD, Stanford V or BEACOPPesc regimens with or without ISRT. Recent studies have evaluated the role of positron emission tomography (PET) adapted algorithms to help guide treatment decisions in high-risk HD patients. Such adapted strategies can identify which patients benefit from more intensive treatments. In the Response-Adapted Therapy in Advanced Hodgkin's Lymphoma (RATHL) study, a repeat PET scan was done after 2 cycles of ABVD (PET2). Patients with a negative PET2 were randomized to either 4 additional cycles of ABVD or de-escalation of therapy to 4 additional cycles of doxorubicin, vinblastine, and dacarbazine (AVD). Those with a PET2 that was positive received more intense therapy with either BEACOPP-14 or BEACOPPesc. The study supported the de-escalation of ABVD to AVD and the AVD arm was associated with less pulmonary toxicity.[20] The HD18 study performed PET2 in patients after 2 cycles of BEACOPPesc with those who are negative being randomized to 4 *vs.* 6 or 8 additional cycles of BEACOPPesc, with the difference in the 5-year PFS being 1.4%, (95% *CI*: −2.7 to 5.4), the arm that received 4 cycles also had fewer infections or organ toxicities.[21] Investigations into the role of de-escalating therapy with the omission of radiotherapy based on PET2 in early-stage HD were not successful.[22]

Brentuximab with a chemotherapy backbone

After decades of ABVD, Stanford V and BEACOPP/BEACOPPesc being the preferred regimens for HD, the newest practice changing advancement in the care of untreated HD came with the presentation of the ECHELON-1 study. This was a phase III study that compared ABVD to BV with doxorubicin, vinblastine, and dacarbazine (BV + AVD) in patients with stage III and stage IV HD. Six hundred and seventy patients were assigned to the ABVD arm and 664 patients were assigned to the BV + AVD arm. The primary endpoint was modified PFS and the main secondary endpoint was OS. Patients in the BV + AVD arm received BV 1.2 mg/kg, doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2 and dacarbazine 375 mg/m^2. Patients in the ABVD arm got doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2 and dacarbazine 375 mg/m^2 on days 1 and 15 of a 28-day cycle, for a total of 6 cycles. The incidences of neutropenia and febrile neutropenia were 58% and 19% respectively in the BV + AVD group and 45% and 8% in the ABVD group. The rates of grade 3 neuropathy and pulmonary toxicity were 11% and 2% respectively in the BV + AVD group and 2% and 7% respectively in the ABVD group. There were 9 deaths in the BV + AVD group (7 due to neutropenia and 2 due to myocardial infarction). In the ABVD group, there were 13 deaths (11 due to pulmonary toxicity and 1 due to cardiorespiratory issues and for 1 the cause was not known). After a median follow-up of 24.6 months, the modified PFS was 82.1% (95% *CI*, 78.8−85.0) versus 77.2% (95% *CI*, 73.7−80.4) and the hazard ratio for death, progression or modified progression was 0.77 (95% *CI*, 0.60−0.98; $P = 0.04$) favoring the BV + AVD group. Subgroup analysis showed patients from North America, male patients, those younger than 60 years, patients with more than one extranodal site of involvement, those with an International Prognostic Score (IPS) between 4 and 7, and those with stage IV disease seemed to benefit from BV + AVD.[23] Based on this study, the United States Food and Drug Administration (FDA) has approved the BV + AVD combination in patients with stage III and IV HD. Given the benefit of BV in North American patients, and impressive clinical efficacy despite the omission of bleomycin from the ABVD backbone, BV + AVD is poised to become the first-line regimen of choice for the treatment of HD in North America. Future studies to evaluate the BV + AVD versus BV + BEACOPPesc like regimens are warranted given the emerging survival data supporting BEACOPPesc.[14,21]

The NCT01868451 study investigated the BV + AVD combination in untreated early-stage unfavorable risk HD. Patients received 4 cycles of BV + AVD followed by ISRT. Twenty-five patients received BV + AVD followed by 30 Gy ISRT. All 25 patients who completed BV + AVD + ISRT achieved a complete response (CR) and the one-year PFS was 93.3% after a median follow-up of 18.8 months.[24] In a second cohort of this study, the ISRT dose was reduced to 20 Gy to reduce toxicity with similar results.[25] This study suggests that this combination is highly effective in patients in the early-stage setting in addition to the advanced-stage setting.

The ongoing German Hodgkin Study Group HD21 (NCT02661503) study is evaluating the role of BV in patients with advanced HD and will compare BrECADD (BV, etoposide, doxorubicin, cyclophosphamide, dacarbazine, dexamethasone) to BEACOPPesc. The BrECADD arm was chosen as the experimental arm for this study due to its favorable toxicity profile compared to BrECAPP (BV, etoposide, doxorubicin, cyclophosphamide, procarbazine and prednisone) in a phase II study comparing the regimens.[26] Originally, the study assigned patients in both study arms to 6 cycles of treatment; however, based upon the results of the HD15 trial, a PET adapted approach after 2 cycles was implemented.[27] Patients will receive two cycles of treatment with either BrECADD or BEACOPP and undergo a staging fluorodeoxyglucose (FDG)-PET scan. Based upon the PET2 results, participants will receive a total of 4 or 6 cycles of their assigned treatment regimens.

In alignment with recent PET-adapted approaches for the treatment of HD, the COBRA (NCT03517137) study is a single armed phase II study being planned by the European Organization for Research and Treatment of Cancer (EORTC). All patients will receive one cycle of BV + AVD followed by a PET scan. Patients with a negative early scan will continue with five more BV + AVD cycles for a total six cycles, while patients with a positive PET would go to receive six cycles of BrECADD.

Other studies have evaluated the efficacy of replacing consolidative radiation therapy with BV. NCT01578967 is a phase II trial of ABVD followed by BV consolidation in non-bulky limited-stage HD. In this study, patients with limited-stage HD received 2 to 6 cycles of ABVD based on risk factors and interim PET results, followed by BV every 3 weeks for 6 cycles. Ninety percent of the patients achieved PET negativity after completion of BV.[28] Another phase II study (NCT01534078) examined the use of BV plus AVD for non-bulky limited-stage HD and avoided the

use of bleomycin and radiation. In this study, patients received a lead in cycle of BV on days 1 and 15, followed by 4–6 cycles of BV plus AVD. Thirty-four patients were enrolled and after a median follow-up of 14 months, the PFS and OS are 90% and 97%.[29]

Yet other studies are investigating de-escalating therapy in older and frailer patients with the addition of BV and omitting other agents to reduce toxicity. The BREVITY study (NCT02567851) was a phase II study that evaluated use of single agent BV in patients with HD who were not fit to receive standard therapy because of age, frailty or other medical comorbidities. The primary outcome of this study was complete metabolic response (CMR). Of the 31 patients evaluable for response, the CMR was 26% and the overall objective response rate (ORR) was 84% with a median PFS of 7.4 months.[30]

NCT01716806 is an open-label, multicenter, phase II clinical trial designed to evaluate the efficacy and safety of BV as a single-agent (Part A), with dacarbazine (Part B), bendamustine (Part C), or nivolumab (Part D) in front-line therapy of HD in adults aged 60 and above. Of the 27 patients enrolled in Part A, the ORR was 92%, with 73% CR rate and a median PFS of 10.5 months.[31] Twenty two patients were enrolled on Arm B (BV + dacarbazine). The ORR in Arm B was 100% with a CR rate of 62% and a median PFS of 17.9 months. Arm C (BV + bendamustine) was closed because of serious adverse event (AE) including deaths. For this arm, the ORR was 100% and the CR rate was 88%.[32]

Other chemotherapy trials that are in progress for upfront therapy in older frailer patients include NCT02505269 (BV + doxorubicin + dacarbazine), NCT03576378 BrEPEM-LH-22017 (BV + cyclophosphamide + procarbazine + etoposide + mitoxantrone and prednisone), NCT02191930 (BV + cyclophosphamide + doxorubicin + prednisolone) and NCT02414568 (bendamustine + prednisone + vinblastine + doxorubicin).

In addition to BV and chemotherapy combinations, several immune checkpoint inhibitors are currently being tested as a single agent, in combination with BV, and in combination with chemotherapy.

Management of relapsed disease

Traditionally, the management of relapsed or refractory disease included salvage chemotherapy followed by high-dose therapy and stem cell rescue (autologous stem cell transplant) and, in some cases, an allogeneic transplant. The development of BV as well as immune checkpoint inhibitors have revolutionized viable therapeutic options for this group of patients.

BV

BV has drastically altered the management of relapsed and refractory HD. It is currently being used as salvage treatment in the relapsed and refractory setting as well as maintenance therapy in the post-autologous stem cell transplant period.

In the pivotal phase II study (NCT00848926) of BV in patients with relapsed or refractory HD after high-dose therapy and autologous stem cell transplant, patients received BV at a dose of 1.8 mg/kg, once every 3 weeks for up to 16 cycles. Of the 102 patients enrolled in the study, 34% achieved a CR, with an ORR of 75%. At 5 years, the estimated OS rate was 41% and the PFS rate was 22%. For those in CR, the OS rate was 64% and PFS rate was 52% and the median OS and PFS had not been reached at 5 years. Thirteen patients were in CR at the time of study closure, 4 of whom underwent an allogeneic transplant and 9 remained in CR without any additional therapy. Based upon these results, BV was approved by the FDA for use in patients who have failed 2 or more prior lines of therapies, who were not eligible for an autologous stem cell transplant, and those who relapsed after an autologous stem cell transplant.[33,34]

Subsequently, BV was evaluated in the setting of post-transplant maintenance. The AETHERA study (NCT01100502) was a phase III randomized double-blind, placebo-controlled study which compared BV to placebo in patients with a high risk of relapse post-autologous stem cell transplant. High risk was defined as either primary refractory disease, initial duration of remission less than 1 year, or an extranodal site of relapse at any time. Three hundred and twenty-nine patients were randomized to receive either BV ($n = 164$) or placebo ($n = 165$). Those on BV received it at a dose of 1.8 mg/kg once every 3 weeks for a maximum of 16 cycles. The median PFS was 42.9 months in the BV arm and 24.1 months in the placebo arm. At 3 years, the PFS rate was 61% for the BV arm and 43% for the placebo arm.[35,36] This led to the FDA approving the drug as maintenance therapy in patients with relapsed/refractory HD who are at high risk of relapse post-autologous stem cell transplant.

Given its efficacy in upfront, relapsed/refractory and post-autologous stem cell transplant setting, BV is now being studied either alone or in combination with other drugs in the relapsed/refractory and in the upfront setting. Table 1 is a listing of currently ongoing clinical trials of BV.

Checkpoint inhibition

The discovery that HD is associated with 9p24.1 amplification and hence increased PD-L1, PD-L2 expression, has led to several clinical studies assessing the use of immune checkpoint inhibitors in targeting the PD1-PD-L1/PD-L2 axis. The United States FDA has currently approved checkpoint inhibitors, nivolumab and pembrolizumab, in the management of relapsed/refractory HD.

Nivolumab is a fully human monoclonal immunoglobulin G4 (IgG4) antibody that targets PD-1. The landmark CheckMate 205 (NCT01592370) was a phase II study which enrolled 243 patients in 3 cohorts: Cohort A consisted of 63 patients who were BV naïve, Cohort B consisted of 84 patients who received BV consolidation post-autologous transplant, and Cohort C consisted of 100 patient who received BV before and/or after autologous transplant. Patients received nivolumab at a dose of 3 mg/kg every 2 weeks until progression or unacceptable toxicity. After a median follow-up of 18 months, the ORR was 69%, the CR rate was 16%, and the median PFS was 14.7 months. Forty-four patients went on to receive an allogeneic transplant; however, the median PFS and OS had not been reached for these patients. Seventy patients were treated beyond disease progression (by

Table 1
Currently ongoing clinical trials of BV in the treatment of HD.

Regimen	Eligibility	Type	Name	Results
BV	Elderly HD patients at first relapse or with primary refractory disease	Phase II	NCT02227433	−
BV + Everolimus	Relapsed/refractory	Phase I	NCT02254239	−
BV + Ibrutinib	Relapsed/refractory	Phase II	NCT02744612	69% ORR, 46% CR[37]
BV Q3weeks ×12	Post-allogeneic transplant consolidation	Phase II	NCT03540849	−
BV Q3weeks ×4	Post-allogeneic transplant consolidation	Phase I/II	NCT02098512	−
BV *vs*. Pembrolizumab	Relapsed/refractory	Phase III	NCT02684292 (KEYNOTE-204)	−
BV ×8 cycles after 2 cycles of e-BEACOPP and IFRT	Patients with stage I/II HD who are PET positive after 2 cycles of ABVD	Phase II	NCT02298283	−
BV + Bendamustine	First salvage	Phase I/II	NCT01874054	$n = 55$, 92.5% ORR, 73.6% CR[38]
BV + Lenalidomide	Relapsed/refractory	Phase IB	NCT03302728	−
BV + Mocetinostat (MGCD0103 an HDAC inhibitor)	Relapsed/refractory, not eligible for transplant	Phase IB/II	NCT02429375	−
BV + Nivolumab	Relapsed/refractory	Phase I/II	NCT02572167	$n = 62$, 61% CR, 82% ORR[17]
BV + Nivolumab	Consolidation after autologous stem cell transplant	Phase II	NCT03057795	−
BV + Umbralisib (TGR-1202 PI3K delta inhibitor)	Relapsed/refractory after an autologous stem cell transplant or at least 2 lines of therapy	Phase I/IB	NCT02164006	$n = 14$, 45% CR, 64% ORR, 50% of BV refractory patients responded[39]
BV + DHAP	Pre-transplant salvage	Phase I/II	NCT02280993	−
BV + ESHAP	Pre-transplant salvage	Phase II	NCT02243436	$n = 66$, 96% ORR, 26% CR[40]
BV + ICE	Pre-transplant salvage	Phase I/II	NCT02227199, NCT02686346	94% ORR, 88% CR by investigator review, 69% CR by central review (NCT02227199)[41]
BV *vs*. BV + Nivolumab	Relapsed/refractory	Phase III	NCT03138499 (CheckMate 812)	−
BV + MDR1 inhibitor (cyclosporine/verapamil)	Relapsed/refractory	Phase I	NCT03013933	−

BV: brentuximab vedotin; HD: Hodgkin's Disease; ORR: objective response rate; CR: complete response; Q; every; e-BEACOPP: escalated dose of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; IFRT: involved field radiation therapy; PET: positron emission tomography; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; MGCD0103: mocetinostat; HDAC: histone deacetylase; PI3K: phosphoinositide 3-kinase; DHAP: cisplatin, cytarabine, and dexamethasone; ESHAP: etoposide, methylprednisolone, cytarabine and cisplatin; ICE: ifosfamide, carboplatin and etoposide; MDR1: multidrug resistance receptor 1; −: not available.

conventional criteria) and 61% of those patients had further reduction in target lesion size or stabilization. There were no treatment related deaths. The most common AEs of any grade were fatigue (23%), diarrhea (15%) and infusion reaction (14%). The most common grade 3–4 AEs were elevated lipase (5%), neutropenia (3%) and elevated alanine aminotransferase (ALT; 3%).[19]

Pembrolizumab is a humanized IgG4 antibody, like nivolumab, which targets PD-1 and is the second immune checkpoint inhibitor approved for use in relapsed/refractory HD. This approval was based upon the results of the KEYNOTE-087 (NCT02453594) study. In this study two hundred and ten patients were enrolled into 3 cohorts. Cohort 1 included sixty-nine patients who progressed after autologous stem cell transplant and BV, cohort 2 included eighty-one patients who failed salvage chemotherapy and BV with no transplant, and cohort 3 had sixty patients who relapsed after an autologous transplant but did not receive BV. Patients received pembrolizumab at a dose of 200 mg intravenously every 3 weeks for 24 months or until progression or unacceptable toxicity. The ORR, by blinded independent central review across all the cohorts, was 69% with a CR rate of 22.4%. More than 90% of the patients had a reduction in the burden of disease. The most common AE of any grade was hypothyroidism (12.4%) and pyrexia (10.5%). The most common grade 3–4 AEs were neutropenia (2.4%), dyspnea (1%) and diarrhea (1%). There were two deaths but this was thought to be unrelated to pembrolizumab.[42]

In addition to the studies mentioned above, pembrolizumab, nivolumab and several other checkpoint inhibitors are in clinical trials in the upfront setting as well as the relapsed/refractory setting (Table 2).

Table 2
Ongoing checkpoint inhibitor trials in the treatment of HD.

Regimen	Eligibility	Type	Name	Results
Nivolumab	Bridge to transplant in patients with relapsed/refractory disease	Phase II	NCT03337919 (ANIMATE)	–
Nivolumab + BV	Consolidation post-autologous transplant	Phase II	NCT03057795	–
Pembrolizumab + ISRT	Early-stage relapsed/refractory	Phase II	NCT03179917	–
Nivolumab + AVD × 4 → IFRT *vs.* Nivolumab × 4 → Nivolumab + AVD × 2 → AVD × 2 → IFRT	Early-stage unfavorable classical HD	Phase II	NCT03004833	–
Pembrolizumab	Inadequate response to frontline chemotherapy	Phase II	NCT03407144	–
Nivolumab + Low dose radiotherapy	Incomplete responders	Phase II	NCT03495713 (Radvax)	–
Nivolumab	Localized RT to progressive lesion	Phase II	NCT03480334 (AERN)	–
Nivolumab Q2wks ×12	Maintenance post-autologous transplant	Phase II	NCT03436862	–
Pembrolizumab	Post-autologous transplant	Phase II	NCT02362997	–
Pembrolizumab + ICE	Pre-transplant salvage	Phase II	NCT03077828	–
Nivolumab + Bendamustine	Relapsed/refractory	Phase I/II	NCT03343652	–
Nivolumab + BV	Relapsed/refractory	Phase I/II	NCT02572167	$n = 62$, 61% CR, 82% ORR[17]
Pembrolizumab + Lenalidomide	Relapsed/refractory	Phase I/II	NCT02875067	–
Pembrolizumab + RP6530 (PI3K δ/γ Dual Inhibitor)	Relapsed/refractory	Phase I/II	NCT03471351	–
SHR-1210 *vs.* SHR-1210 + Decitabine	Relapsed/refractory	Phase I/II	NCT03250962[43]	–
Avelumab	Relapsed/refractory	Phase IB	NCT02603419 (JAVELIN HODGKINS)	–
Pembrolizumab + AFM13	Relapsed/refractory	Phase IB	NCT02665650 (KEYNOTE-206)[44]	–
CS1001	Relapsed/refractory	Phase II	NCT03505996	–
KL-A167	Relapsed/refractory	Phase II	NCT03580564	–
Nivolumab + Ibrutinib	Relapsed/refractory	Phase II	NCT02940301	–
Nivolumab + Lenalidomide	Relapsed/refractory	Phase II	NCT03015896	–
SHR-1210	Relapsed/refractory	Phase II	NCT03155425	–

(*continued on next page*)

Table 2 (*continued*)

Regimen	Eligibility	Type	Name	Results
Sintilimab (IBI308)	Relapsed/refractory	Phase II	NCT03114683 (ORIENT-1)	74% ORR and 24% CR[45]
Tislelizumab (BGB-A317)	Relapsed/refractory	Phase II	NCT03209973	−
Pembrolizumab *vs.* BV	Relapsed/refractory	Phase III	NCT02684292 (KEYNOTE-204)	−
Nivolumab + ABVD	Upfront	Phase I/II	NCT03033914	−
Avelumab→ ABVD or BEACOPP based on PET	Upfront	Phase II	NCT03617666	−
Nivolumab + AVD + BV	Upfront	Phase II	NCT03233347	−
Pembrolizumab + AVD	Upfront	Phase II	NCT03331341, NCT03226249	−
Pembrolizumab	Upfront unfit	Phase II	NCT03331731	−
Nivolumab *vs.* Nivolumab + Vinblastine	Upfront unfit or older than 60 years	Phase II	NCT03580408	−
Nivolumab + BV	Upfront unfit or older than 60 years	Phase II	NCT02758717	−
Nivolumab + BV *vs.* BV	Relapsed/refractory	Phase III	NCT03138499 (CheckMate 812)	−
Nivolumab + ICE	Pre-transplant salvage	Phase II	NCT03016871 (NICE Trial)	−
Pembrolizumab + anti-LAG3 antibody MK-4280	Relapsed/refractory	Phase I/II	NCT03598608	−
Pembrolizumab + NG-monomethyl-L-arginine (L-NMMA)	Melanoma, non-small-cell lung cancer, head and neck squamous cell carcinoma, classical HD, urothelial carcinoma, or microsatellite instability-high/mismatch repair deficient tumors	Phase IB	NCT03236935	−
Nivolumab + EBVSTs	Relapsed/refractory EBV positive lymphoma patients	Phase I	NCT02973113 (PREVALE)	−

HD: Hodgkin's Disease; BV: brentuximab vedotin; ISRT; involved site radiation therapy; AVD: doxorubicin, vinblastine, and dacarbazine; IFRT: involved field radiation therapy; RT: radiotherapy; Q2wks: every 2 weeks; ICE: ifosfamide, carboplatin and etoposide; CR: complete response; ORR: objective response rate; PI3K: phosphoinositide 3-kinase; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; PET: positron emission tomography; LAG3; lymphocyte-activation gene 3; EBVSTs: Epstein-Barr virus-specific T cells; EBV: Epstein-Barr virus; −: not available.

Bispecific antibodies

AFM-13 is a bispecific antibody and is a tetravalent construct which binds CD30 on CD30 positive cells and CD16A expressed on natural killer (NK) cells.[46] In a phase I (NCT0122157) dose escalation study of patients with relapsed/refractory HD, 11.5% of patients had a partial response (PR) and 50% had stable disease with a disease control rate of 61.5%.[47] GHSG-AFM13 (NCT02321592) is a Phase II trial with AFM13 in patients with relapsed or refractory HD. NCT02665650 (KEYNOTE-206) is a phase II trial of pembrolizumab and AFM13 in patients with relapsed/refractory disease.[44] Results from the above studies are still pending and it remains to be seen if this drug becomes as successful as blinatumomab, a bispecific antibody effective in CD19 positive acute lymphoblastic leukemia (ALL).

Small molecules

mTOR inhibitors

In HD there is activation of the phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) pathway. Hodgkin cell lines have shown high levels of AKT activation and phosphorylation of downstream targets.[48] NCT01022996 is a phase II study using everolimus (RAD001) in patients with relapsed/refractory HD. Fifty-seven patients were enrolled in this study. Everolimus was given at a dose of 10 mg daily until progression or unacceptable toxicity. The ORR was 45.6%, the CR rate was 8.8% and 36.8% of patients had a PR. The median PFS was 8 months. The drug was well tolerated and the common AEs were thrombocytopenia (45.6%), fatigue (31.6%), anemia (26.3%), rash (24.6%), and

stomatitis (22.8%).[49] Further clinical studies are currently ongoing with various combinations of everolimus in the relapsed/refractory setting (NCT01453504 in combination with cisplatin, cytarabine, and dexamethasone [DHAP], NCT02254239 in combination with BV).

Janus kinase (JAK) inhibitors

As described above, HD is often associated with 9p24.1 amplification, and this leads to amplification and increased expression of PD-L1 and PD-L2. The 9p24.1 locus also includes the JAK2 locus. Of note, JAK activation can induce PD-L1 transcription.[50] Clinical studies (NCT01965119, NCT01877005) evaluating ruxolitinib, a JAK inhibitor, in patients with relapsed/refractory HD have shown modest responses both in HD and primary mediastinal B cell lymphoma.[51,52] Other studies are currently ongoing (NCT02164500, NCT02613598).

Bruton tyrosine kinase Inhibitors (BTK)

Case reports have shown that ibrutinib maybe be potentially beneficial in relapsed/refractory HD.[53] Such effect is assumed to be secondary to interleukin-2-inducible T-cell kinase (ITK) mediated mechanisms.[54] In a phase II study (NCT02744612) of ibrutinib in combination with BV, the ORR was 69% and the CR rate was 46%.[37] Other studies of ibrutinib as a single agent (NCT02824029) as well as in combination with nivolumab (NCT02940301) are ongoing.

Lenalidomide

Lenalidomide is thought to be helpful in the setting of hematologic malignancies through its immunomodulatory as well as anti-angiogenic effects.[55] In a phase II study of lenalidomide in 38 patients with relapsed/refractory HD (NCT00540007), there was an ORR of 19% with one CR.[56] Other clinical trials are ongoing to evaluate the combination with anti-PD-1 antibodies (NCT03015896-nivolumab, NCT02875067-pembrolizumab) as well as BV (NCT03302728). Lenalidomide is also being studied as a post-autologous stem cell transplant maintenance strategy (NCT01207921).

Cellular therapy

While the large majority of the cellular therapy trials are early phase trials, they seem to hold a great deal of promise in terms of efficacy. Such cellular therapies include antigen specific cytotoxic T cells and CART therapy.

Cytotoxic T cells

About 30%–40% of HD tends to be EBV positive. Administration of EBV specific cytotoxic T cells has shown to be effective to treat patients with EBV positive disease resulting in sustained responses.[57] Several clinical studies which evaluate EBV specific cytotoxic T lymphocytes (CTLs) (NCT02763254, NCT01956084, NCT01555892), with EBV specific CTLs expressing chimeric CD30 receptors (NCT01192464), most closely matched EBV specific third party CTLs (NCT02287311, NCT01447056), PD-1 knockout EBV-CTLs (NCT03044743), along with nivolumab (NCT02973113) and tumor-associated antigen (TAA)-specific CTLs are currently ongoing.

CD30 chimeric antigen receptor T cell (CD30 CART) therapy

CD19 CART cells have revolutionized the management of $CD19^{+}$ ALL as well as diffuse large B cell lymphomas. In a phase I study (NCT01316146), CD30 CART cells were utilized in patients with HD and anaplastic large cell lymphoma. Two of seven patients with HD went into a CR and three had transient stable disease.[58] In another CART study (NCT02259556) of 18 HD patients treated, seven achieved a PR and six patients had stable disease, without significant toxicities.[59] Other studies are currently ongoing (NCT03383965, NCT02917083).

Conclusion

The treatment armamentarium of HD has rapidly evolved beyond traditional cytotoxic chemotherapy regimens over the past several years. While ABVD and BEACOPPesc remain the standard of care for the treatment of HD, both have limitations in terms of acute and long-term toxicities. The evolving role of agents such as brentuximab and checkpoint inhibitors in the relapsed/refractory setting is encouraging. Additionally, it is encouraging to see a number of ongoing trials evaluating the role of these agents in various combinations and with other treatment modalities earlier in the treatment of HD. Further studies are needed to evaluate the appropriate sequence of these novel agents in HD. With the adoption of PET guided therapy, identifying which patient could benefit from such therapies will be of great importance. In North America, it is very likely that within a few years BV + AVD may be the new standard therapy for the treatment of HD and BV has an evolving role in combination with BEACOPP like regimens in Europe.

Conflict of interest

None declared.

References

1. Cartwright RA, Watkins G. Epidemiology of Hodgkin's disease: a review. *Hematol Oncol*. 2004;22:11–26.
2. Hodgkin. On some morbid appearances of the absorbent glands and spleen. *Med Chir Trans*. 1832;17:68–114.
3. Yahalom J, Mauch P. The involved field is back: issues in delineating the radiation field in Hodgkin's disease. *Ann Oncol*. 2002;13 Suppl 1:79–83.
4. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). *Int J Radiat Oncol Biol Phys*. 2014;89:854–862.
5. Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ, Gilman A, McLennan MT. Nitrogen mustard therapy; use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. *J Am Med Assoc*. 1946;132:126–132.
6. Carbone PP, Spurr C, Schneiderman M, Scotto J, Holland JF, Shnider B. Management of patients with malignant lymphoma: a comparative study with cyclophosphamide and vinca alkaloids. *Cancer Res*. 1968;28:811–822.
7. Devita VT Jr, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med*. 1970;73:881–895.
8. Bonadonna G, Zucali R, Monfardini S, de Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer*. 1975;36:252–259.
9. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med*. 2003;348:2386–2395.
10. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med*. 2011;365:203–212.
11. Carde P, Karrasch M, Fortpied C, et al. Eight cycles of ABVD versus four cycles of BEACOPPescalated plus four cycles of BEACOPPbaseline in Stage III to IV, International Prognostic Score $\geq$ 3, high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 Intergroup Trial. *J Clin Oncol*. 2016;34:2028–2036.
12. Vijenthira A, Cheung MC, Phua CW, et al. ABVD versus combination baseline beacopp/escalated beacopp in the treatment of newly diagnosed advanced-stage Hodgkin lymphoma: a decision analysis. *Blood*. 2016;128:1183.
13. Jiang Y, Chen Y, Huang R, Chen G. Comparison of the efficiency of ABVD versus BEACOPP for Hodgkin lymphoma treatment: a meta-analysis. *Int J Hematol*. 2016;104:413–419.
14. Skoetz N, Will A, Monsef I, Brillant C, Engert A, von Tresckow B. Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma. *Cochrane Database Syst Rev*. 2017;5:CD007941.
15. Bartlett NL, Rosenberg SA, Hoppe RT, Hancock SL, Horning SJ. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. *J Clin Oncol*. 1995;13:1080–1088.
16. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol*. 2013;31:684–691.
17. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131:1183–1194.
18. Scott LJ. Brentuximab vedotin: a review in CD30-positive Hodgkin lymphoma. *Drugs*. 2017;77:435–445.
19. Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. *J Clin Oncol*. 2018;36:1428–1439.
20. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced hodgkin's lymphoma. *N Engl J Med*. 2016;374:2419–2429.
21. Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet*. 2018;390:2790–2802.
22. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med*. 2015;372:1598–1607.
23. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV hodgkin's lymphoma. *N Engl J Med*. 2018;378:331–344.
24. Kumar A, Casulo C, Yahalom J, et al. Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma. *Blood*. 2016;128:1458–1464.
25. Kumar A, Casulo C, Advani RH, et al. A pilot study of brentuximab vedotin and AVD chemotherapy followed by 20 Gy involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma. *Blood*. 2017;130(Suppl 1):734.
26. Eichenauer DA, Plütschow A, Kreissl S, et al. Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin's lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. *Lancet Oncol*. 2017;18:1680–1687.
27. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012;379:1791–1799.
28. Park SI, Olajide O, Reddy NM, et al. Brentuximab vedotin consolidation to reduce radiation use in patients with limited stage non-bulky Hodgkin lymphoma: an update from a phase 2 clinical trial. *Hematol Oncol*. 2017;35(S2):81–82.
29. Abramson JS, Arnason JE, LaCasce AS, et al. Brentuximab vedotin plus AVD for non-bulky limited stage Hodgkin lymphoma: A phase II trial. *J Clin Oncol*. 2015;33(15_suppl):8505.
30. Gibb A, Pirrie S, Linton K, et al. Results of a phase II study of brentuximab vedotin in the first line treatment of Hodgkin lymphoma patients considered unsuitable for standard chemotherapy (BREVITY). *Hematol Oncol*. 2017;35(S2):80–81.

31. Forero-Torres A, Holkova B, Goldschmidt J, et al. Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older. *Blood*. 2015;126:2798–2804.
32. Friedberg JW, Forero-Torres A, Bordoni RE, et al. Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥60 years with HL. *Blood*. 2017;130:2829–2837.
33. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's Lymphoma. *J Clin Oncol*. 2012;30:2183–2189.
34. Chen R, Gopal AK, Smith SE, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2016;128:1562–1566.
35. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015;385:1853–1862.
36. Sweetenham JW, Walewski J, Nadamanee A, et al. Updated efficacy and safety data from the AETHERA trial of consolidation with brentuximab vedotin after autologous stem cell transplant (ASCT) in Hodgkin lymphoma patients at high risk of relapse. *Biol Blood Marrow Transplant*. 2016;22:S36–S37.
37. Chen RW, Palmer JM, Herrera AF, et al. Phase II study of brentuximab vedotin plus ibrutinib for patients with relapsed/refractory Hodgkin lymphoma. *Blood*. 2017;130(Suppl 1):738.
38. LaCasce AS, Bociek RG, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;132:40–48.
39. Ramchandren R, Mulroney CM, Patel MR, Sportelli P, Miskin HP, Chen RW. A phase I trial of TGR-1202, a next generation once-daily PI3Kδ inhibitor, in combination with brentuximab vedotin, in patients with relapsed/refractory Hodgkins lymphoma. *Blood*. 2016;128:4146.
40. Garcia-Sanz R, Sureda A, Gonzalez AP, et al. Brentuximab vedotin plus ESHAP (BRESHAP) is a highly effective combination for inducing remission in refractory and relapsed Hodgkin lymphoma patients prior to autologous stem cell transplant: a trial of the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO). *Blood*. 2016;128:1109.
41. Cassaday RD, Fromm J, Cowan AJ, et al. Safety and activity of brentuximab vedotin (BV) plus ifosfamide, carboplatin, and etoposide (ICE) for relapsed/refractory (Rel/Ref) classical Hodgkin lymphoma (cHL): initial results of a phase I/II trial. *Blood*. 2016;128:1834.
42. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol*. 2017;35:2125–2132.
43. Wang C, Liu Y, Nie J, Shen L, Yang Q, Han W. Safety and efficacy of decitabine-primed anti-PD-1 (SHR-1210) treatment in patients with relapsed/refractory classical Hodgkin lymphoma. *J Clin Oncol*. 2018;36(15_suppl):7537.
44. Ansell SM, Chen RW, Forero-Torres A, et al. A phase 1 study investigating the combination of AFM13 and the monoclonal anti-PD-1 antibody pembrolizumab in patients with relapsed/refractory Hodgkin lymphoma after brentuximab vedotin failure: data from the dose escalation part of the study. *Blood*. 2017;13:1522.
45. Shi Y, Su H, Song Y, et al. Sintilimab (IBI308) in relapsed/refractory classical Hodgkin lymphoma: A multicenter, single-arm phase 2 trial in China (ORIENT-1 study). *J Clin Oncol*. 2018;36(15_suppl):7536.
46. Wu J, Fu J, Zhang M, Liu D. AFM13: a first-in-class tetravalent bispecific anti-CD30/CD16A antibody for NK cell-mediated immunotherapy. *J Hematol Oncol*. 2015;8:96.
47. Rothe A, Sasse S, Topp MS, et al. A phase 1 study of the bispecific anti-CD30/CD16A antibody construct AFM13 in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2015;125:4024–4031.
48. Dutton A, Reynolds GM, Dawson CW, Young LS, Murray PG. Constitutive activation of phosphatidyl-inositide 3 kinase contributes to the survival of Hodgkin's lymphoma cells through a mechanism involving Akt kinase and mTOR. *J Pathol*. 2005;205:498–506.
49. Johnston PB, Pinter-Brown LC, Warsi G, White K, Ramchandren R. Phase 2 study of everolimus for relapsed or refractory classical Hodgkin lymphoma. *Exp Hematol Oncol*. 2018;7:12.
50. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116:3268–3277.
51. Kim SJ, Kang HJ, Dong-Yeop S, et al. The efficacy of JAK2 inhibitor in heavily pretreated classical Hodgkin lymphoma: a prospective pilot study of ruxolitinib in relapsed or refractory classical Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2016;128:1820.
52. Van Den Neste E, André M, Gastinne T, et al. A phase II study of the oral JAK1/JAK2 inhibitor ruxolitinib in advanced relapsed/refractory Hodgkin lymphoma. *Haematologica*. 2018;103:840–848.
53. Hamadani M, Balasubramanian S, Hari PN. Ibrutinib in refractory classic hodgkin's lymphoma. *N Engl J Med*. 2015;373:1381–1382.
54. Dubovsky JA, Beckwith KA, Natarajan G, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. *Blood*. 2013;122:2539–2549.
55. Kotla V, Goel S, Nischal S, et al. Mechanism of action of lenalidomide in hematological malignancies. *J Hematol Oncol*. 2009;2:36.
56. Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. *Blood*. 2011;118:5119–5125.
57. Bollard CM, Gottschalk S, Torrano V, et al. Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. *J Clin Oncol*. 2014;32:798–808.
58. Ramos CA, Ballard B, Zhang H, et al. Clinical and immunological responses after CD30-specific chimeric antigen receptor-redirected lymphocytes. *J Clin Invest*. 2017;127:3462–3471.
59. Wang CM, Wu ZQ, Wang Y, et al. Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory Hodgkin lymphoma: an open-label phase I trial. *Clin Cancer Res*. 2017;23:1156–1166.

Edited by Pei-Fang Wei