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Risk-adapted chemoimmunotherapy using brentuximab vedotin and rituximab in children, adolescents, and young adults with newly diagnosed Hodgkin's lymphoma: a phase II, non-randomized controlled trial

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ABSTRACT

Background Cure rates for Hodgkin's lymphoma are excellent, but excess short-term and long-term morbidities from treatment remain a concern. Immunotherapy targeting both tumor antigens and the immunosuppressive tumor microenvironment in children, adolescents, and young adults with Hodgkin's lymphoma may improve early response rates and eliminate toxic chemotherapy and radiation, thus minimizing toxicity. We conducted a phase II study to evaluate the safety and overall response rate of brentuximab vedotin and rituximab in combination with risk-adapted chemotherapy in children, adolescents, and young adults with newly diagnosed classic Hodgkin's lymphoma (cHL).

Methods This is a prospective, phase II, non-randomized, risk-assigned study. Patients were treated and evaluated between 2012 and 2020. Eligible patients were aged ≥1 and ≤30 years old with advanced stage, intermediate-risk, and high-risk newly diagnosed cHL. Patients received four or six cycles of brentuximab vedotin (1.2 mg/kg), doxorubicin (25 mg/m^2), vinblastine (6 mg/m^2), dacarbazine (375 mg/m^2), and rituximab (375 mg/m^2). Early response was evaluated following two cycles of therapy. Involved field radiotherapy (IFRT) was restricted to high-risk patients with both bulky disease and slow response or those not in complete response at the end of chemoimmunotherapy.

Results Thirty patients were enrolled, with a median age of 15 years (4–23). There were 18 intermediate-risk and 12 high-risk patients. Toxicities included grade III mucositis (3%), infusion reaction (3%), and peripheral neuropathy (6%). There was a 100% complete response rate on completion of chemoimmunotherapy. Eighteen patients (60%) achieved a rapid early response. Four patients (13%) required IFRT. The 5-year event-free and overall survival rates were 100%, with a median follow-up of 62 months (18–105).

Conclusions Immunotherapy with brentuximab vedotin, rituximab, and risk-adapted chemotherapy is safe in children, adolescents, and young adults with newly diagnosed cHL. We have demonstrated 100% complete response and 100% event-free and overall survival rates at a median 5-year follow-up, with a significant reduction in use of more toxic chemotherapy and IFRT. A larger cohort is required to confirm these preliminary findings.

Trial registration number NCT02398240.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Overall cure rates for Hodgkin's lymphoma are excellent, but there are notable excess short-term and long-term morbidities following therapy, with a high rate of grades 3–5 adverse health conditions in pediatric and young adult patients later in life, and are compounded by using multiple toxic chemotherapy regimens in combination with radiation therapy.

⇒ Immunotherapy for Hodgkin's lymphoma has demonstrated excellent response rates in the relapsed and refractory settings, leading to multiple upfront trials in both adult and pediatric cooperative groups.

WHAT THIS STUDY ADDS

⇒ To our knowledge, this trial is the first to characterize the safety, tolerability, and activity of the combination of brentuximab vedotin and rituximab with reduced toxicity chemotherapy backbone and elimination of radiation therapy for majority of children, adolescents, and young adults with newly diagnosed, advanced stage Hodgkin's lymphoma.

⇒ Our trial provides data that immunotherapy with both brentuximab vedotin and rituximab along with risk-adapted chemotherapy is safe in children, adolescents, and young adults with newly diagnosed classic Hodgkin's lymphoma, with a demonstrated 100% complete response and 100% event-free and overall survival at a median 5-year follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The addition of immunotherapy targeting both the CD30-positive Reed-Sternberg cell with brentuximab vedotin as well as the CD20-rich tumor microenvironment with rituximab provides promising early response rates, with a very high rate of durable complete remission despite a drastic reduction in the use of involved field radiotherapy.
⇒ Omission of several toxic chemotherapy agents within the backbone as well as limiting exposure to radiotherapy provide excellent overall outcome and may eliminate late effects potentially arising from chemoradiotherapy.
⇒ The survival outcomes of patients in our study compare favorably with data from currently published controlled trials.
⇒ This new treatment strategy warrants further investigation on a larger scale and provides a backbone for further immunotherapy studies.

INTRODUCTION

While cure rates in children, adolescents, and young adults (CAYA) with newly diagnosed classic Hodgkin's lymphoma (cHL) treated with multiagent chemotherapy regimens and involved field radiotherapy (IFRT) remain high, there are significant late effects secondary to chemoradiotherapy.[1] A personalized approach based on risk factors, response-based therapy, and incorporation of targeted agents with improved toxicity profiles is needed.[1]

Chemoradiotherapy regimens have been directly associated with both short-term and long-term toxicities, with the incidence of grades 3–5 adverse health conditions >15% in adult survivors of childhood cHL.[2 3] Radiation therapy has been shown to further compound the risk of late mortality, obesity, and organ dysfunction, with worsening effects on cardiovascular, pulmonary, and thyroid function.[4] The risk of development of secondary cancers, particularly in organs exposed to radiation fields, remains elevated 35 years or more after treatment, with a cumulative incidence of a second cancer being close to 50%.[5]

Hodgkin Reed-Sternberg (HRS) cells derive from germinal center B cells.[6] While typically comprising less than 1%–5% of tumor cellularity, HRS cells are surrounded by a heterogeneous inflammatory infiltrate characterized by T cells, B cells, natural killer (NK) cells, and mast cells.[6] This tumor microenvironment (TME) promotes the survival of HRS cells by delivering multiple survival signals through secretion of multiple cytokines.[6 7] CD30 is highly expressed on the HRS cell, making it an attractive target.[8] In addition, studies have shown that reactive and suppressive regulatory B cells represent up to 50% of infiltrating cells in the TME.[9] Thus, there is possible benefit to targeting suppressive CD20+ regulatory B cells in the cHL TME, even in patients whose HRS cells lack CD20 expression (figure 1).

Brentuximab vedotin (Bv) is a CD30-targeted antibody conjugated to a potent antitubulin agent which selectively induces apoptosis in Hodgkin lymphoma (HL) cells.[10] Pivotal studies have demonstrated the efficacy of Bv in patients with relapsed/refractory cHL,[11 12] as well as phase I safety studies in patients with newly diagnosed, advanced stage cHL.[13 14] Adult cHL relapse studies[15 16] as well as phase II studies in newly diagnosed, advanced stage cHL treated with the anti-CD20 monoclonal antibody rituximab (375 mg/m^2) in combination with standard chemotherapy regimens have demonstrated excellent event-free and overall survival (EFS and OS) with minimal additional toxicities.[17 18] However, although response rates have been excellent, studies to date have not demonstrated clear survival benefit with the addition of rituximab to combination therapy regimens.

The challenge for CAYA with cHL is the need to significantly reduce long-term toxicity of successful combination chemoradiotherapy while continuing to demonstrate superior survival. Current efforts in clinical trials involve better risk stratification of patients, de-escalation of therapy in the setting of rapid early response (RER), and adaptation of novel targeted therapies targeting the Hodgkin's lymphoma Reed-Sternberg cell and the immune suppression regulated by the TME. This pilot study was designed to investigate the safety of combinatorial immunotherapy with Bv and rituximab added to a risk-adapted multiagent chemotherapy backbone in CAYA patients with newly diagnosed, intermediate-risk and high-risk cHL that specifically omitted cyclophosphamide, etoposide,

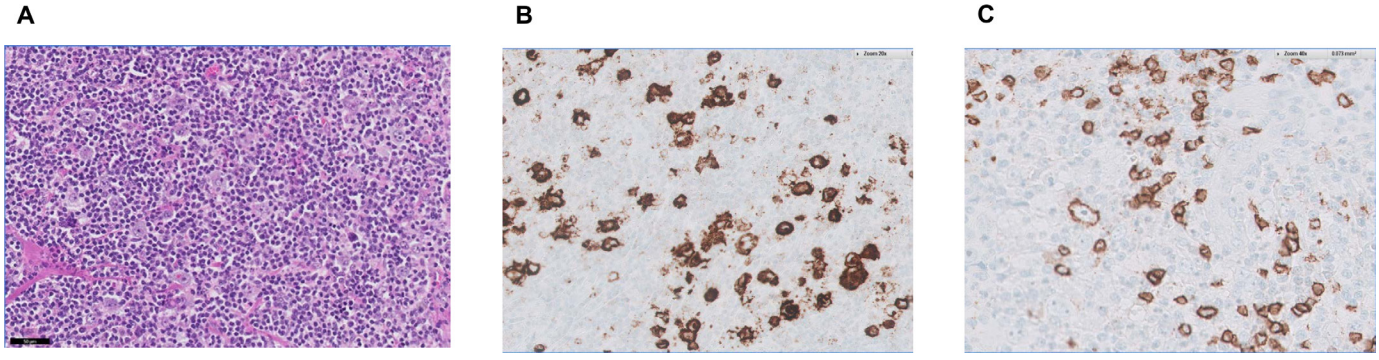


Figure 1 Immunohistochemistry in a classic Hodgkin's lymphoma. (A) A patient demonstrating CD30 positivity on the surface of Reed-Sternberg cells (B) and CD20 (C) staining weakly positive on a few large cells, with strong positivity on the surrounding reactive and regulatory B cells.

bleomycin, procarbazine, and prednisone from the treatment regimen. We hypothesized this approach would also allow for a significant reduction in IFRT as well as reduction in more toxic chemotherapy exposure, while providing excellent survival with less overall morbidity in CAYA with newly diagnosed higher stage cHL.

PATIENTS AND METHODS

Patients

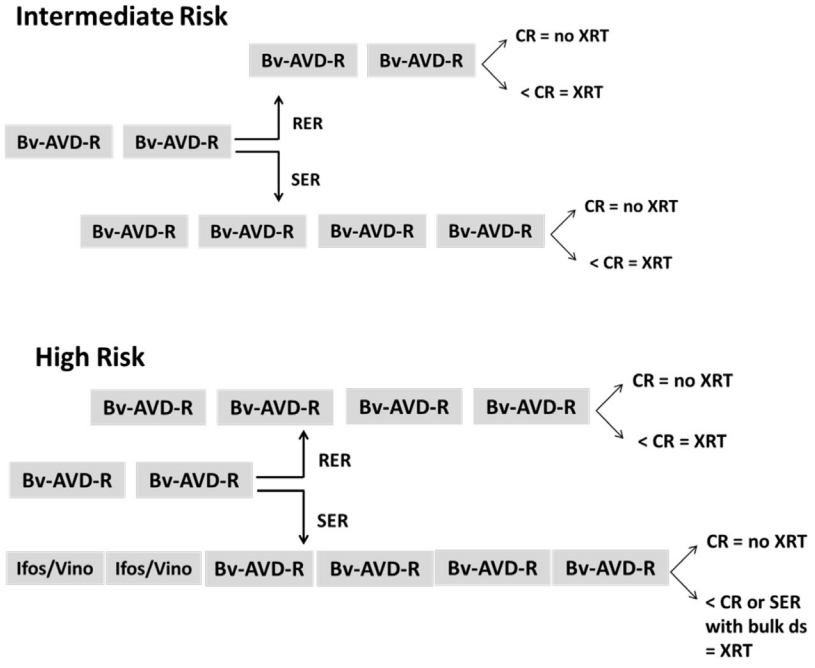
Patients aged ≥1 to ≤30 years with newly diagnosed cHL were eligible. Staging was determined by the Lugano classification with modifiers for bulky disease, extension, and B symptoms.[19] Bulky disease was defined as mediastinal tumor diameter greater than one-third the thoracic diameter or any extramediastinal nodal aggregate >6 cm in the longest transverse diameter. Intermediate-risk patients were stage IA bulk/E, IB, IIA bulk/E, IIB, and IIIA. High-risk patients were stage IIB bulk/E, IIIA bulk/E, IIIB, and IVA/B. Patients required adequate organ function and performance status. No prior cHL-directed therapy was allowed except for emergent irradiation (<1000 cGy) for superior vena cava syndrome. Patients or legally authorized guardians were required to sign informed consent in accordance with institutional policies approved by the US Department of Health and Human Services. The study was registered at ClinicalTrials.gov (NCT02398240) (online supplemental information).

Treatment

Chemoimmunotherapy for both intermediate-risk and high-risk patients consisted of Bv 1.2 mg/kg/dose, doxorubicin 25 mg/m^2/dose, vinblastine 6 mg/m^2/dose, and dacarbazine 375 mg/m^2/dose on days 1 and 15. Rituximab 375 mg/m^2/dose was given on days 2 and 16 (figure 2). Patients were supported with filgrastim until neutrophil count recovery. Intermediate-risk patients deemed RER after two cycles of chemoimmunotherapy received two additional cycles for a total of four cycles of therapy and no planned radiation. Intermediate-risk patients deemed slow early responders (SER) after two cycles of chemoimmunotherapy received an additional four cycles for a total of six cycles. IFRT was considered at the end of six cycles and given only to those intermediate-risk patients *not* in complete response (CR) at the end of six cycles of chemoimmunotherapy. High-risk patients deemed RER after two cycles of chemoimmunotherapy received four more cycles for a total of six cycles of therapy and no planned radiation. High-risk patients deemed SER after two cycles of chemoimmunotherapy received an additional two cycles of therapy consisting of ifosfamide 3000 mg/m^2/day on days 1–4 and vinorelbine 25 mg/m^2/dose on days 1 and 5, as previously described, prior to resuming the remaining four cycles of Bv and rituximab chemoimmunotherapy for a total of eight cycles of therapy. IFRT was considered at the end of eight cycles and given only to those *not* in CR or to high-risk patients who presented with initial bulky disease and found to be slow responders, regardless of remission status at the end of chemoimmunotherapy.

Radiation therapy

IFRT was given to patients who were not in CR after completion of all planned chemoimmunotherapy. In addition, IFRT was given to high-risk patients with initial



Drug Name	Dose	Days Given
Brentuximab vedotin	1.2mg/kg	1, 15
Doxorubicin	25mg/m^2	1, 15
Vinblastine	6mg/m^2	1, 15
Dacarbazine	375mg/m^2	1, 15
Rituximab	375mg/m^2	2,16
Ifosfamide	3,000mg/m^2	1-4
Vinorelbine	25mg/m^2	1-5

Figure 2 Treatment schema for intermediate-risk and high-risk patients with cHL. Bv-AVD-R, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine, rituximab; cHL, classic Hodgkin's lymphoma; CR, complete response; Ifos, ifosfamide; RER, rapid early responder; SER, slow early responder; Vino, vinorelbine; XRT, radiation therapy; ds, disease.

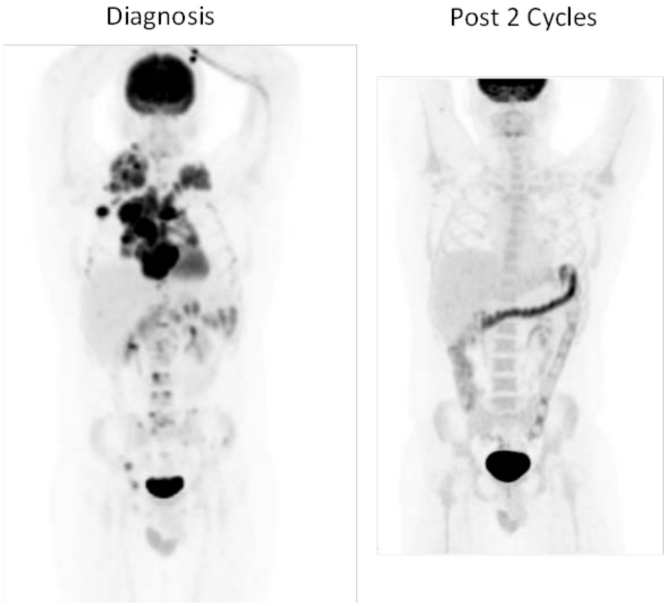


Figure 3 FDG-PET imaging showing early response following two cycles of Bv-AVD-R in a patient with stage IV, high-risk, classic Hodgkin's lymphoma. AVD-R, doxorubicin, vinblastine, dacarbazine, rituximab; Bv, brentuximab vedotin; FDG-PET, fluorodeoxyglucose-positron emission tomography.

bulky disease who were determined to be SER. IFRT was *not* given to intermediate-risk patients based on bulky disease alone or to any intermediate-risk or high-risk patients regardless of initial bulky disease who were found to be RER. For eligible patients, IFRT consisted of 21 Gy in 14 fractions of 1.50 Gy per day given 5 days per week over a 2.8-week period. All fields were treated once daily. IFRT treatment began no later than 4 weeks after completion of the last cycle of chemotherapy or when blood counts had recovered. IFRT treatment was limited to areas of disease defined as bulky at initial presentation using standard techniques and clinical target volumes.

Disease evaluation and response definitions

Disease evaluation with CT scan of the neck, chest, abdomen, and pelvis as well as positron emission tomography (PET)/CT was performed at diagnosis for all patients. All patients underwent ^{18}F-fluorodeoxyglucose (FDG)-PET/CT scan following two cycles of chemoimmunotherapy in order to determine early treatment response (figure 3). RER was defined as having achieved CR at this time point. CR was defined based on both anatomical and functional imaging criteria and required resolution of pathological palpable lymphadenopathy and at least 80% reduction in the product of the perpendicular diameters of each of the nodal masses, no residual disease in non-measurable evaluable lesion sites, no new lesion(s), and a negative FDG-PET/CT (Deauville score ≤3). SER was defined as partial response (PR) or stable disease. PR was defined as at least 50% reduction in the product of the perpendicular diameter of each of the areas of measurable disease but not constituting a CR, with no new lesion(s). FDG-PET/CT could be positive (Deauville score of 4 or 5) at original sites of disease or could be negative. Progressive disease was defined as at least 50% increase in the product of the perpendicular diameter of any of the involved nodes or nodal masses or development of new lesion(s). Stable disease was defined as less than a PR but not progressive disease. Patients underwent subsequent FDG-PET/CT at the completion of therapy and at regular intervals in follow-up for up to 3 years. Bone marrow aspiration/biopsy was performed at diagnosis, during early response assessment, and at the end of therapy if previously positive. Quantitative immunoglobulin and peripheral blood CD19 and CD3 levels were evaluated at a median of 18 months of follow-up.

Statistical analyses

Patients were considered evaluable for both toxicity and survival analysis if they received at least one dose of Bv. The point estimate of percentage with exact 90% CI was used to evaluate the overall CR and PR rate. The Kaplan-Meier survival function with 90% CI was used to determine EFS proportion. An event was defined as any disease progression, recurrence, or death. A one-sided alpha of 0.1 was used in calculating stopping boundaries for safety and efficacy. The O'Brien-Fleming boundary method was used to calculate stopping boundaries. The plus-four method was used to calculate the CI. We planned accrual of 10 high-risk patients as the primary group and a maximum of 20 intermediate-risk patients as the secondary group. A 1-year EFS not less than 75% was established as the primary stopping boundary in the high-risk group (online supplemental table 1) and not less than 80% in the intermediate-risk group (online supplemental table 2).

RESULTS

Patient characteristics

The median age was 15 years (range, 4–23 years), with a female to male ratio of 18:12. Disease risk included 18 intermediate-risk and 12 high-risk patients. A total of 12 patients presented with bulky disease and 12 patients presented with B symptoms, and some with both. There were six stage IIA, eight stage IIB, five stage IIIA, one stage IIIB, seven stage IVA, and three stage IVB patients (table 1).

Safety

All patients completed the planned chemoimmunotherapy. There were a total of four (13%) grade 3 or greater non-hematological adverse events that occurred. These included two (6%) grade 3 neuropathy, one (3%) grade 3 allergic reaction to Bv, and one (3%) grade 3 mucositis. There were no dose-limiting toxicities encountered. Immune profiles at a median of 18 months of follow-up demonstrated IgG level of 1140±63 mg/dL, absolute CD19 level of 424±62 cells/µL, and absolute

Table 1 Patient characteristics

Demographics	Patients (N=30)	%
Age, median	15 (4–23 years)	
Female	18/30	60
Male	12/30	40
Ann Arbor stage		
Stage I	0/30	0
Stage II	14/30	47
B symptoms*	8/14	57
Bulky disease*	6/14	43
Neither	0/14	0
Stage III	6/30	20
B symptoms*	1/6	17
Bulky disease*	2/6	33
Neither	3/6	50
Stage IV	10/30	33
B symptoms*	3/10	30
Bulky disease*	4/10	40
Neither	4/10	40
Risk assignment		
Intermediate	18/30	60
High	12/30	40

*One or both.

Table 2 Response outcomes stratified by risk

	Intermediate risk (n=18)		High risk (n=12)	
	n	%	n	%
Early response				
Rapid	14	78	4	25
Slow	4	22	8	75
PET2 negative	18	100	10	83
Final response				
Complete	18	100	12	100
Partial	0		0	
PET negative	18	100	12	100

PET, positron emission tomography.

CD3 level of 1485±186 cells/µL (all within normal range) (figure 4).

Efficacy

All 30 (100%) patients achieved CR on completion of chemoimmunotherapy. RER was observed in 18 patients (60%). When stratified by risk group, 78% of the intermediate-risk and 25% of the high-risk patients met the criteria for RER (table 2). Of note, of patients with SER, 83% were FDG-PET-negative by Deauville scoring but did not meet the strict size reduction criteria of 80% to be considered a rapid response. However, all slow responders met the CR criteria on completion of planned chemoimmunotherapy. Only 4 of 30 (13%) patients underwent radiation therapy per protocol requirements. All were high-risk patients found to be SER with bulky disease. However, each patient was in CR prior to radiotherapy. The EFS/OS for all patients was 100%, with a median follow-up time of 62 months (range, 18–106 months) (figure 5).

DISCUSSION

Despite excellent outcomes in CAYA cHL, acute and long-term toxicities still remain a significant challenge. In this study, we demonstrated that Bv and rituximab combined with risk-adapted chemotherapy were safe and feasible in CAYA with newly diagnosed cHL. Furthermore, majority of the patients (87%) avoided IFRT and 100% of the patients achieved long-term EFS and OS with a median 5-year follow-up. Historically, this group of patients has required cyclophosphamide, procarbazine, etoposide, bleomycin, and/or IFRT to multiple sites to achieve similar results.

The ECHELON-1 trial demonstrated superior results in adult patients with advanced stage cHL, using

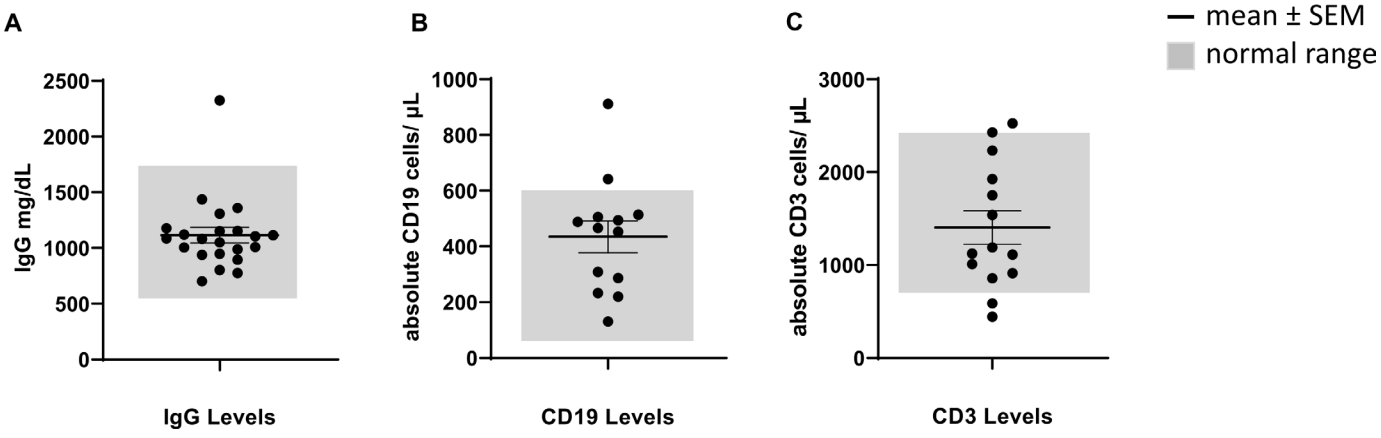


Figure 4 Mean±SEM IgG (A), absolute CD19 (B) and absolute CD3 (C) levels at a median of 18 months of follow-up.

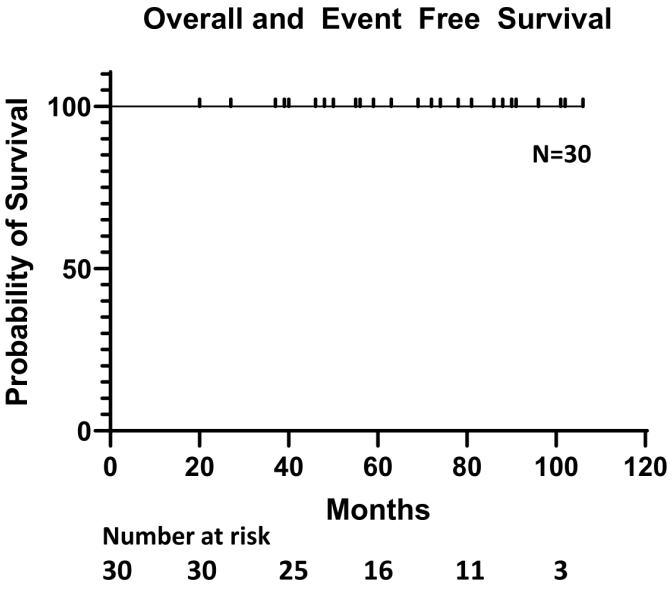


Figure 5 Probability of event-free and overall survival by the product limit method of Kaplan-Meier.

combination Bv, doxorubicin, vinblastine, and dacarbazine, compared with standard doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). They demonstrated 5-year progression-free survival rates in the A+AVD and ABVD groups of 82.2% vs 75.3%, with a beneficial trend in patients in the Bv group who still had residual FDG-avid disease after two cycles of therapy.[20] This landmark trial led to Food and Drug Administration approval for Bv in combination with chemotherapy as front-line treatment in adult advanced cHL. Our trial adds to the ECHELON-1 data, demonstrating the safety and efficacy of this approach in CAYA patients while adding the novelty of using two immunotherapy agents targeted to both tumor cells and the immunosuppressive TME to achieve a more rapid and complete response, thus obviating the need for radiation therapy in younger patients. Several pediatric studies are ongoing which also combine Bv with combination chemotherapy in patients with advanced stage cHL. Results of the recently completed St Jude's Hodgkin's multicenter consortium trial incorporating brentuximab to replace vincristine into each of six cycles of traditional OEPA (Oncovin, etoposide, prednisone, and Adriamycin)/COPDac (cyclophosphamide, Oncovin, prednisone, dacarbazine) backbone chemotherapy have demonstrated overall safety, tolerability, and efficacy of this approach, with 3-year EFS of 97.4% and OS of 98.7%.[21] In our pilot study, we were also able to demonstrate the safety and tolerability of combining Bv with risk-adapted chemotherapy with the elimination of etoposide, bleomycin, cyclophosphamide, and procarbazine from the chemotherapy backbone. Patients were supported with granulocyte colony-stimulating factor, which allowed chemotherapy cycles to be given without delay. Immune profiles in our study returned to normal in all patients measured post chemoimmunotherapy. Adverse events were minimal in our study, with the most common being peripheral neuropathy, similar to that seen in adult studies. Only two patients (6%) developed a grade 3 neuropathy requiring dose reduction of Bv. All patients with neuropathy of any grade had complete resolution of symptoms on completion of therapy.

Adult studies using rituximab-ABVD for advanced cHL have investigated the percentage of patients with clonotypic B cells.[18] They found clinical efficacy, with 81% of patients attaining CR, with 3-year EFS and OS rates of 83% and 98%, respectively.[18] Long-term follow-up of these patients has not shown survival improvement over standard ABVD; however, survival measures alone do not determine the full benefit of this approach.[22] In the adult study, only 8% of patients received radiation therapy. In addition, Epstein-Barr virus copy numbers showed a rapid decline in patients with Epstein-Barr virus+ tumors. Finally, the study was able to determine that persistence of detectable circulating clonotypic B cells was associated with a greater relapse frequency ($p<0.05$).[18] The implications of rituximab in eliminating regulatory B cells within the cHL TME are currently unknown. Certainly, EFS and OS have not been clearly affected in longer term studies with the addition of rituximab. It also remains unknown what additional benefit rituximab offers when included in regimens containing Bv. Our data suggest that rituximab may play a role in cHL by potentially inhibiting suppressive regulatory B cells. In the St Jude's brentuximab study mentioned above, the trial design gave residual node radiotherapy of 25.5 Gy to all patients with nodal sites who did not achieve complete early response following two cycles of therapy. While they were able to effectively decrease the total number of targeted sites, only 35% of patients achieved CR at this early benchmark and were spared radiation.[21] Our study demonstrated a 100% EFS at a median 5-year follow-up, with only 13% of patients requiring IFRT. The role of rituximab may in fact be to increase the number of patients achieving RER, thus eliminating the need for IFRT even in patients with bulky advanced disease. Comparing the results of our trial with the results of the completed ECHELON-1 study or ongoing pediatric studies with Bv-containing chemoimmunotherapy without rituximab may provide some evidence of what role, if any, rituximab is adding to our regimen.

The addition of radiation therapy to combination chemotherapy compounds adverse health effects in CAYA patients with HL.[4] An analysis by Mulrooney *et al*[23] demonstrated the risk of myocardial ischemia increased with higher radiation doses, with an overall HR of more than 12 for those treated with mediastinal radiotherapy in childhood. Effects on pulmonary and thyroid function show similar patterns.[4 24 25] It is known that cHL survivors are at risk of developing secondary malignancies.[26] The risk of secondary leukemia tends to be low in patients treated with current Hodgkin's treatment protocols. However, this risk increases significantly in regimens which combine drugs such as etoposide and increased doses of alkylating agents along with radiation.[27] Solid

tumor malignancies present much more of a concern, with the highest incidence being treatment-related breast cancer in women, followed by lung cancer in men, as well as thyroid cancers in both, reflecting history of mantle radiation exposure in patients.[28] Women treated with chest radiotherapy for cHL have a strongly elevated risk of developing breast cancer compared with the general population.[29] The risk appears inversely related to age at the time of treatment and is highest for women who are exposed to radiotherapy during puberty.[30] There needs to be a coordinated effort to eliminate IFRT for most children, adolescent, and young adult patients with cHL to address these many long-term health needs. Our study demonstrates that we were able to achieve a high percentage of patients (60%) with RER to therapy. Only those patients with high-risk bulky disease and SER were required to undergo IFRT, which included four patients (13%) in our cohort. Notably, we used a very conservative definition of RER, requiring both PET negativity as well as at least 80% reduction in tumor size by CT scan. If we had relied on PET2 negativity only, as is the approach in many current studies, 28 of 30 patients (93%) would have met the criteria for RER and only 2 patients would have required IFRT. In addition, adult studies use end-of-therapy PET results to determine further therapy needs. In our study, all 30 patients achieved a PET-negative CR at the end of chemoimmunotherapy cycles, regardless of early response. Using updated criteria, this would have translated into none of the patients (0%) requiring IFRT in our study. This is in contrast to other current clinical trials in CAYA cHL where a high percentage of intermediate-risk and high-risk patients continue to meet the criteria for radiotherapy.

This study also emphasizes the now common practice of eliminating surveillance imaging. Based on our current protocols at the time of study development and concern for possible early relapse, patients enrolled in this pilot study underwent FDG-PET/CT imaging following completion of therapy at regular intervals for up to 3 years. Given 100% of patients achieved CR at completion of chemoimmunotherapy and we have not demonstrated any concern for relapse to date, there is support to forego off-therapy surveillance imaging studies for patients, particularly those who achieve early treatment response milestones.

The results of this study are promising, although small in number. We have shown that the combination of both Bv and rituximab immunotherapy can be safely combined with risk-adapted chemotherapy. We were able to eliminate prednisone, bleomycin, cyclophosphamide, procarbazine, and etoposide without compromising response or outcomes. More importantly, we have eliminated IFRT for 87% of patients and likely able to further limit the need for radiation to close to zero in the future. One area that we seek to improve on is limiting anthracycline dose. Our patients received between 200 mg/m^2 and 300 mg/m^2 of doxorubicin based on response. This remains above the 150–250 mg/m^2 that many contemporary protocols use. A major objective in our follow-up study is to investigate limiting doxorubicin dose to no more than 100 mg/m^2 for all patients by using an enhanced immunotherapy regimen. In addition, we recognize the potential toxicity of giving ifosfamide/vinorelbine to high-risk slow responders. While ifosfamide/vinorelbine was well tolerated with minimal acute toxicities in the eight patients in the study who received it, longer term toxicities are unknown. Our follow-up study will eliminate these two cycles of ifosfamide/vinorelbine as it is likely not needed given the achievement of complete metabolic responses seen in intermediate-risk slow responders with just additional chemoimmunotherapy cycles.

Further comparisons with other Bv-containing regimens will be needed to assess the efficacy of this approach in a larger CAYA population as well as the impact of the addition of rituximab. Future studies will additionally be required to determine whether the antilymphoma activity of this chemoimmunotherapy backbone, potentially in combination with other agents such as checkpoint inhibitors, might allow for further reduction of more toxic chemotherapy agents (particularly anthracyclines). Our results support the use of this regimen upfront in a larger cohort of CAYA patients with newly diagnosed cHL to confirm these preliminary findings. Longer follow-up of this cohort will be required to determine if there is a reduction of late effects compared with historical controls treated with more toxic chemoradiotherapy regimens.

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Contributors Study conception and design: JH, MSC, LK, and QS. Patient accrual and management on study: JH, MSC, AF, HI, CM, and PG. Accrual and assembly of data: JB, KB, LH, and CvdV. Data analysis and interpretation: JH, MSC, QS, and SV. Manuscript preparation and writing: JH and MSC. JH and MSC had full access to all the data in this study and take full responsibility for the integrity of the data and accuracy of the data analysis. All authors are accountable for all aspects of this work and approved the final draft and submission of the manuscript. Guarantors: JH and MSC.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the New York Medical College Institutional Review Board (NYMC-568). Participants gave informed consent to participate in the study before taking part.

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