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Symposium Report

2016 BMT TANDEM MEETINGS

Examining Targeted Therapies for Hodgkin Lymphoma in the Post-Transplant Setting: Reason for Optimism

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Program Overview

Hodgkin lymphoma (HL) is a pathologically and clinically heterogeneous hematologic malignancy. In the United States, an estimated 185,000 people are currently living with this disease, and it accounted for more than 9,000 new cases of cancer in 2015. Chemotherapy and radiation provide long-term benefit to the majority of patients with HL; however, some patients will eventually relapse.

High-dose chemotherapy followed by autologous stem cell transplant (ASCT) is the standard of care for relapsed disease, resulting in complete remission rates of approximately 50%. However, patients who relapse after ASCT generally have poor outcomes, with 5-year overall survival rates as low as 12% in patients with multiple poor prognostic factors. In an attempt to prolong the benefit of ASCT in relapsed/refractory HL, chemotherapy and targeted therapy regimens have been tested as consolidation therapy. However, finding an appropriate balance between efficacy and tolerability has remained challenging. Since therapy options in the relapsed/refractory setting are limited, the discovery of new, well-tolerated agents that may

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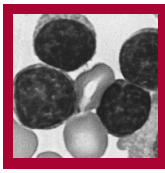

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improve the benefit of ASCT has been a high priority.

One of the most recent therapies to be approved for the management of HL was brentuximab vedotin. This antibody-drug conjugate combines an anti-CD30 monoclonal antibody with a cytotoxic chemotherapy to deliver a targeted, cytotoxic payload to tumor cells. In its pivotal study for HL treatment, brentuximab vedotin demonstrated high response rates and favorable overall survival in patients who had failed prior chemotherapy and ASCT. More recently, researchers have explored brentuximab vedotin as consolidation therapy post-ASCT. The results of this study showed that brentuximab vedotin improves progression-free survival in patients with risk factors for progression with manageable toxicity.

Researchers also have placed a high priority on discovering factors that can help predict the risk of relapse following ASCT. Such a risk assessment would help identify patients for whom consolidation therapy should be considered. Fluorodeoxyglucose-positron emitting tomography (FDG-PET) has been established as an important prognostic tool for early HL. More recently, however, it has been studied as a tool for assessing the risk of ASCT failure. Specifically, patients with residual HL detectable by FDG-PET after high-dose chemotherapy are at greater risk for progression following ASCT.

Learning Objectives

Upon completion of the program, participants should be able to:

1. Define patients with high-risk Hodgkin Lymphoma (HL) due to known risk factors both at the time of initial diagnosis, as well as the relapsed/refractory setting
2. Describe the role of interim fluorodeoxyglucose-positron emission tomography (FDG-PET) to assess responsiveness of the disease to therapy
3. Consider which patients may be candidates for targeted consolidation therapy post-autologous stem cell transplant (ASCT)
4. Discuss the targeted therapies currently approved or in clinical trials for post-transplant therapy

Target Audience

This activity has been developed and is intended for hematologists, oncologists, bone marrow transplant (BMT) specialists and other healthcare professionals involved in the treatment of patients with HL.

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Jack W. Hsu, MD, has no relevant financial relationships to disclose.

John R. Wingard, MD, has no relevant financial relationships to disclose.

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LETTER FROM THE EDITOR

Relapsed Hodgkin's Lymphoma: New Approaches for a Difficult Problem

Jack W. Hsu and John R. Wingard, University of Florida College of Medicine, Gainesville, FL

Hodgkin's lymphoma is a rare, highly curable lymphoma with a worldwide incidence of 66,000 cases per year. Over 80% of patients are cured with modern therapies. For the approximately 20% of patients with relapsed or refractory disease, there is no standard therapy. The typical paradigm involves salvage chemotherapy followed by stem cell transplant. Unfortunately, for patients with relapsed Hodgkin's lymphoma, the success rate for cure is low, ranging from 25% to 40%. For patients who relapse after transplant, the options for treatment are very limited.

There is optimism, however, for patients who have relapsed Hodgkin's lymphoma. Use of FDG-PET scans prior to transplantation can help identify patients who may require more intensive chemotherapy to optimize their disease status prior to autologous transplant. New prognostic models of factors present either before or after autologous transplantation can identify patients who will respond well with autologous transplant and allow patients who are predicted to respond poorly. These will allow clinicians to avoid ineffective therapy and identify patients who may benefit from novel approaches.

Increased understanding of the pathophysiology of Hodgkin's disease has also led to the development of targeted therapies which can improve the outcomes of high risk patients after autologous transplant. The ATHERA trial was the first trial to show improvement in progression free survival with maintenance therapy after autologous transplant. New drug classes, such as PD-1 inhibitors, either alone or in combination with chemotherapy or with other targeted therapies, hold promise to improve the survival of patients with relapsed disease.

In this transcript of a a satellite symposium held in February 2016 at the Tandem BMT meeting in Honolulu, HI, Dr. Stephen Ansell discusses the prognosis of patients with relapsed Hodgkin's disease and the new prognostic models developed to identify high risk patients before and after transplantation. Dr. John Sweetenham discusses new salvage therapies that are available for patients with relapsed Hodgkin's disease. Relapsed Hodgkin's disease, especially after autologous transplant, is an important unmet medical need in oncology. Our increased understanding of the pathophysiology of Hodgkin's disease and how to risk- stratify our patients is allowing for greater precision in effectively treating this disease. The development of targeted therapies is bringing new hope for patients in this especially difficult to treat population.

Introduction

Stephen Ansell, MD, PhD

Hodgkin lymphoma (HL) is a highly curable hematologic malignancy, with cure rates of approximately 80% in patients who undergo modern frontline treatment with combination chemotherapy and radiation therapy. The current standard of care for patients with relapsed or refractory HL following frontline treatment involves salvage chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT). Historically, treatment options have been limited for patients who relapse following transplantation. Therefore, the goal of treatment is to minimize the risk of relapse.

Recent research has focused on identifying patients with HL at high risk for relapse, as well as understanding adverse prognostic factors in the relapse setting. Achieving a negative fluorodeoxyglucose-positron emission tomography (FDG-PET) scan prior to ASCT, for example, predicts very favorable post-transplantation outcomes irrespective of the salvage regimen. Based on improved knowledge of the pathophysiology of HL, several novel and highly active new regimens have been developed with the goal of improving cure rates while reducing treatment-related toxicity. Results of recent clinical trials examining these novel agents and regimens in the pre- and post-transplant settings are changing the standard of care for patients with HL.

Defining High Risk for Relapse Following Autologous Stem Cell Transplant: Who are They?

Stephen Ansell, MD, PhD

Approximately 8,500 new cases of HL will be diagnosed each year in the United States, contributing to a worldwide incidence of 66,000 cases annually [1, 2]. In total, HL accounts for 0.5% of all cancers and 0.3% of all cancer deaths, with 25,000 deaths per year [2]. The distribution of patient age at diagnosis is bimodal, with peak incidences at 20 to 24 years and 80 to 84 years. The latter group of elderly patients, who comprise approximately 25% of the overall HL population, are more difficult to treat.

The prognosis of HL is favorable for patients who are diagnosed with early-stage disease, but worsens for patients who are diagnosed at more advanced stages. The 5-year disease-specific survival is 90% for patients with stage I or II HL, but decreases to 84% and 65% for those with stage III and IV disease, respectively.

Classification of Hodgkin Lymphoma

Two major disease classification systems are used to describe HL subtypes. The Rye classification system describes four major subtypes of HL: nodular sclerosis (70%), mixed cellularity (20%), lymphocyte predominant (5%), and lymphocyte depleted (5%). Based on immunophenotyping, the lymphocyte-predominant subtype of HL is clearly a distinct entity when compared with other subtypes. Lymphocyte-predominant HL is characterized by CD20-positive neoplastic cells and a high prevalence of other B cell antigens.

The World Health Organization (WHO) classification system recognizes the fundamental differences between lymphocyte-predominant HL and classical Hodgkin lymphoma (cHL), which vary in clinical presentation, morphology, phenotype, molecular features, and natural history. Within the WHO classification system, cHL is further categorized into the following five subcategories:

- Nodular sclerosis
- Lymphocyte rich
- Mixed cellularity
- Lymphocyte depleted
- Unclassifiable

The unique pathophysiology of cHL provides important insights regarding potential therapeutic targets. Within the typical lymph node biopsy sample, malignant Reed-Sternberg (RS) cells are often scarce, comprising only 1% to 2% of cells within an extensive reactive inflammatory background. However, these neoplastic cells consistently express the CD15 and CD30 antigens. In addition, approximately 30% of RS cells also harbor the Epstein Barr virus.

Recent studies have further characterized the unique molecular signatures of cHL. Additional studies have focused on the programmed death-1 (PD-1) signaling pathway. In their role as immune checkpoint inhibitors, the PD-1 ligands PD-L1 and PD-L2 bind the PD-1 receptor on T cells and induce PD-1 signaling. Activating the PD-1 signaling pathway leads to T-cell exhaustion through reversible inhibition of T-cell activation and proliferation. Tumor cells that express PD-1 ligands are able to exploit the PD-1 pathway to evade the antitumor immune response.

Alterations in the PD-1 signaling pathway are a defining feature of cHL pathophysiology. In one analysis, genetic alterations affecting the PD-1 ligands PD-L1 and PD-L2 were present in 97% of 108 cHL biopsy specimens harvested from patients with newly diagnosed cHL [3]. The type of PD-1 pathway alteration also correlated with cHL disease stage and prognosis. In particular, the chromosome 9p24.1 alteration was highly prevalent in advanced-stage cHL and predicted shorter progression-free survival (PFS) [3]. The high prevalence and prognostic significance of PD-L1 and PD-L2 alterations in cHL provide the rationale for PD-1 pathway blockade as an emerging treatment strategy. Recent studies examining the safety and efficacy of PD-1 inhibition in patients with cHL are summarized in the next section [4].

Prognostic Factors in HL

Early-Stage HL

The European Organization for Research and Treatment of Cancer (EORTC) and German Hodgkin Study Group (GHSG) prognostic scoring systems have identified multiple unfavorable prognostic factors in patients with limited-stage HL (Table 1) [5, 6]. In both scoring systems, the presence of a large mediastinal mass and elevated an erythrocyte sedimentation rate (ESR) in patients with stage I or II HL indicate worse long-term prognosis. The

Table 1. Unfavorable Prognostic Factors in Limited-Stage Hodgkin Lymphoma [5, 6]

EORTC Scoring System	GHSG Scoring System
· Large mediastinal mass	· Large mediastinal mass
· Elevated ESR	· Elevated ESR
· ≥ 3 nodal sites	· ≥ 4 nodal sites
· Extranodal disease	· Age ≥ 50 years
· Massive splenic disease	

EORTC, European Organization for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group.

EORTC scoring system includes three additional unfavorable prognostic factors: 3 or more nodal sites, extranodal disease, and massive splenic disease. By comparison, the GHSG scoring system recognizes two additional poor prognostic factors in patients with early-stage HL: 4 or more nodal sites and age ≥ 50 years.

Advanced-Stage HL

The spectrum of adverse prognostic factors differs slightly in advanced (stage III or IV) HL. In 1998, the International Prognostic Factors Project identified several poor prognostic factors that predict worse PFS and overall survival (OS) in patients with advanced HL [7]. Now the gold standard for risk stratification, the International Prognostic Score (IPS) recognizes the following adverse prognostic features in advanced HL:

- Age ≥ 45 years
- Stage IV disease
- Male sex
- White blood count ≥ 15,000 cells/μL
- Lymphocyte count < 600 cells/μL or < 8%
- Albumin < 4.0 g/dL
- Hemoglobin < 10.5 g/dL

For an individual with advanced HL and no adverse prognostic factors, the estimated 5-year PFS and OS are 84% and 89%, respectively. However, survival estimates decrease with an increasing number of adverse prognostic factors. For instance, for a patient with 2 adverse prognostic factors, such as anemia and stage IV disease, the estimated 5-year PFS and OS are 67% and 81%, respectively. By comparison, for a patient with 5 or more poor prognostic factors, the estimated 5-year PFS and OS are 42% and 56%, respectively [7]. With new treatment options, however, the prognosis for many patients with HL appears to be improving. Emerging agents and more aggressive treatment options are extending PFS and OS, even in those with multiple adverse prognostic factors.

Newly Identified Prognostic Factors

With additional research insights into the pathophysiology of HL, additional biological factors that influence the natural history of HL have been identified [8, 9]. Elevated macrophage and cytokine activity may reflect a more active tumor microenvironment and a more aggressive disease course. One study found a gene signature of tumor-associated macrophages that significantly correlated with primary treatment failure in cHL [8]. In particular, an increased number of CD68+ macrophages correlated with worse PFS. The median PFS for patients with <5%, 0 to 25%, and >25% CD68+ macrophages was not reached, 6.2 years, and 2.7 years, respectively. Furthermore, in patients with limited-stage cHL, the absence of an elevated number of CD68+ macrophages correlated with 100% long-term disease-specific survival. Based on these findings, tumor-associated CD68+ macrophage levels appear to be an important biomarker for risk stratification in cHL [8].

Elevated pretreatment serum levels of interleukin (IL)-6 and IL-2 receptor (IL-2R) also predict worse outcomes in patients with cHL [9]. In a study of 140 patients with cHL, high pretreatment IL-6 levels (P<0.001) and IL-2R levels (P=0.002) significantly predicted early disease relapse and death. Even after standard IPS-based risk stratification, elevated IL-6 and IL-2R levels remained independently predictive of worse treatment outcomes. Furthermore, compared with normal pretreatment cytokine levels or just one high reading (IL-6 or IL-2R), elevated levels of both IL-6 and IL-2R significantly correlated with worse event-free survival (EFS) (P<0.0001). Therefore, pretreatment cytokine profiling may be a useful tool for identifying patients with cHL who are at increased risk for early disease relapse and poor survival [9].

Contemporary HL Treatment Strategies

Approximately 75% to 80% of patients with HL can achieve a cure with modern evidence-based treatment. The choice of primary therapy for HL is driven by the stage of disease and the presence of adverse prognostic factors. The current standard of care involves 2 to 4 cycles of chemotherapy plus involved-field radiotherapy (IFRT) for most patients with early-stage (I and IIA) favorable disease, and 4 cycles of chemotherapy plus IFRT for those with early-stage unfavorable disease. Combination chemotherapy is an appropriate treatment approach for patients with advanced HL.

For the 20% to 25% of patients with HL who will experience disease progression following primary treatment, there is no standard of care for salvage therapy. Over the past 15 years, multiple salvage regimens involving combination chemotherapy followed by HDT/ASCT have been investigated [10]. While overall response rates (ORR) of 70% to 80% are common, complete response (CR) rates tend to range from 25% to 40% [10]. New approaches to salvage therapy are needed to improve outcomes for patients with relapsed HL.

Novel Salvage Therapy in Relapsed HL

Brentuximab vedotin is an anti-CD30 antibody-drug conjugate (ADC) used in patients with CD30-positive HL who relapse after ASCT. Recent trials have examined the role of brentuximab-based combination regimens prior to transplantation in patients with relapsed HL [11, 12]. At the 2015 American Society of Hematology (ASH) annual meeting, investigators from the the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO) presented findings from an ongoing phase I/II trial of brentixumab vedotin plus etoposide, methylprednisolone, cytarabine, and cisplatin (BRESHAP) followed by ASCT in patients with relapsed or refractory

HL [11]. The trial enrolled 27 patients with relapsed/refractory cHL after one prior line of therapy. The BRESHAP salvage regimen was tolerable, with no dose-limiting toxicities. Stem cell mobilization and collection was successful in all eligible patients. The CR rate prior to ASCT was 89% among evaluable patients (n = 9).

Brentuximab vedotin has also shown promising activity in combination with bendamustine in the salvage setting. At the 2015 ASH annual meeting, LaCasce and colleagues presented updated findings from an ongoing phase I/II trial of brentuximab vedotin plus bendamustine in patients with relapsed/refractory cHL [12]. The updated analysis included 55 patients with primary refractory disease (51%) or in first relapse (49%). All patients were treated with brentuximab 1.8 mg/kg plus bendamustine 90 mg/m2 every 3 weeks for up to 6 cycles, following by additional treatment with brentuximab monotherapy for a total of 16 cycles. After completing 2 cycles of brentuximab/bendamustine, patients were eligible to undergo ASCT and then resume single-agent brentuximab consolidation therapy. The ORR was 93% and the CR rate was 74% among 53 patients evaluable for response [12]. The CR rates were similar for patients with primary refractory disease (64%) or relapsed cHL (84%). Responses were highly durable, with an estimated 12-month PFS of 80% for all evaluable patients and for those who proceeded to ASCT (n = 40). The most common adverse events were infusion-related reactions (56%), which were managed with corticosteroids and antihistamine premedication.

Additional brentuximab-based regimens are also under evaluation in other cHL settings. An ongoing phase I/II trial will assess the combination of brentuximab vedotin and nivolumab in approximately 60 patients with relapsed/refractory HL after failure of frontline therapy [13]. In the next section, Dr. Sweetenham will review and discuss the phase III AETHERA trial of consolidation therapy with single-agent brentuximab vedotin in patients at high risk of relapsed following ASCT [14].

Role of ASCT in Hodgkin Lymphoma

For patients with relapsed HL, high-dose chemotherapy followed by ASCT is associated with improved outcomes compared with conventional salvage chemotherapy alone. In 2002, Schmitz and colleagues reported findings from a randomized trial of 161 patients with relapsed HL treated with 2 cycles of dexamethasone and carmustine, etoposide, cytarabine, and melphalan (dexa-BEAM) followed by either 2 additional cycles of dexa-BEAM or high-dose BEAM plus autologous hemopoietic stem cell transplantation (BEAM-HSCT) [15]. Only patients who achieved a complete or partial remission after 2 courses of dexa-BEAM proceeded to additional treatment with dexa-BEAM or BEAM-HSCT. After 3 years, the freedom from treatment failure rate (FFTF) rate was significantly higher in the BEAM-HSCT group compared with dexa-BEAM (55% versus 34%, respectively; P=0.0187). Based on these findings, transplantation appears to significantly prolong FFTF in patients with relapsed chemosensitive HL, regardless of the duration of initial remission.

Prognostic Factors Before Transplant

Prognostic scores are useful tools for predicting the natural history of disease as well as the potential likelihood of benefit from various treatments. The IPI risk score incorporates 7 variables (age, gender, disease stage, serum albumin, hemoglobin, leukocytosis, and lymphocytopenia) to calculate a prognostic score for patients with newly diagnosed HL. In 2002, Beirman and colleagues showed that IPI variables also predict post-transplant outcomes in patients with relapsed HL [16]. In a retrospective review of 379 patients who underwent high-dose chemotherapy followed by ASCT, 4 of the 7 variables in the IPI risk score independently predicted worse EFS and OS. These included age ≥ 45 years, low serum albumin (< 4 g/dL), anemia (Hb < 10.5 g/dL), and lymphocytopenia (lymphocyte count < 600/mm3 or <8% of total white blood cell count). For patients with 0-1, 2-3, or ≥4 of these adverse prognostic features, the estimated 10-year EFS was 38%, 23%, and 7%, respectively. The estimated 10-year OS rates were 48%, 30%, and 15%, respectively.

Building on these findings, Moskowitz and colleagues demonstrated the prognostic significance of a negative FDG-PET scan prior to ASCT in patients with relapsed HL [17]. The phase II trial examined a risk-adapted treatment strategy that used FDG-PET response following salvage therapy to determine whether additional treatment was warranted before proceeding to HDT and ASCT. After 2 cycles of ifosfamide, carboplatin, and etoposide (ICE), patients with a negative FDG-PET scan received transplant (n = 58). Patients with a positive interim FDG-PET scan received 4 additional biweekly doses of gemcitabine, vinorelbine, and liposomal doxorubicin (GVD). Only those patients who achieved a positive FDG-PET scan after GVD proceeded to radiotherapy and HDT/ASCT (n = 17), while those with continued evidence of progressive disease were considered study failures. At a median follow-up of 51 months, the EFS was >80% for patients who had a negative FDG-PET scan after ICE or GVD, compared with 29% for patients with a positive FDG-PET scan (P < 0.001).

Importantly, the presence of extranodal disease correlated with worse outcomes, even among patients who achieved a negative FDG-PET scan [17].

Indeed, 3 distinct cohorts of decreasing EFS probability emerged: FDG-PET-negative patients without extranodal involvement; FDG-PET-negative patients with extranodal involvement; and FDG-PET-positive disease, regardless of the presence of extranodal sites ($P < 0.001$ for trend). Overall, these findings established FDG-PET scan negativity as the goal of salvage therapy for transplant-eligible patients with relapsed HL.

In 2015, Moskowitz and colleagues presented additional data underscoring the importance of negative FDG-PET status prior to ASCT [14]. In the open-label phase II study, patients with relapsed or refractory HL who had failed one prior doxorubicin-based chemotherapy regimen (N = 45) were treated with brentuximab vedotin 1.2 mg/kg on days 1, 8, and 15 every 28 days for 2 cycles. Patients with a negative FDG-PET scan proceeded directly to HDT/ASCT (n = 12). One patient withdrew consent, and 32 patients with a PET-positive scan underwent 2 additional cycles of augmented ICE. Of these, 22 patients achieved PET negativity before proceeding to HDT/ASCT. Overall, 34 of 44 (77%) patients who completed treatment per-protocol were FDG-PET negative before proceeding to HDT/ASCT.

The EFS curves were nearly superimposable for patients who were PET-negative after brentuximab vedotin alone or PET-negative following brentuximab vedotin plus augmented ICE (Table 2), suggesting that achieving PET negativity may be more important for long-term outcomes than the specific salvage regimen used [14]. By comparison, EFS was significantly worse for patients who remained PET-positive following brentuximab vedotin plus augmented ICE. These findings support the use of FDG-PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ICE to achieve a high rate of FDG-PET-negativity in patients with relapsed/refractory HL.

Table 2. Event-Free Survival at 2 Years According to FDG-PET Status and Salvage Treatment Group [14]

	2-Year EFS (95% CI)	P Value
All patients	80% (68% - 92%)	--
FDG-PET-negative after brentuximab vedotin alone	92% (76% - 100%)	0.007
FDG-PET-negative after brentuximab vedotin followed by augmented ICE	91% (79% - 100%)	
FDG-PET-positive after brentuximab vedotin followed by augmented ICE	46% (14% - 78%)	

EFS, event-free survival; FDG-PET, X; ICE, ifosfamide, carboplatin, and etoposide.

Prognostic Factors After Transplant

Favorable treatment outcomes are a possibility for select patients with relapsed/refractory HL following ASCT. However, the presence of adverse prognostic factors decreases the likelihood of treatment success. In a study of 126 patients with HL who relapsed/progressed after their first ASCT, post-relapse management strategies included radiation therapy, chemotherapy with or without radiation therapy, second ASCT, or palliation [18]. After a median of 32 months since relapse/progression, 53 patients (42%) remained alive and 44 patients (35%) remained progression free. An analysis of potential prognostic factors identified 3 variables that significantly correlated with worse survival:

- Presence of B-symptoms
- Pre-ASCT disease refractoriness
- Interval of < 12 months from first ASCT to relapse/progression

Based on these 3 prognostic factors, investigators developed a model to identify patients with a higher (and lower) likelihood of treatment success following post-ASCT relapse/progression. The median OS was 70 months for patients with 0-1 adverse prognostic factors, compared with 17 months for patients with 2-3 factors ($P < 0.001$) [18]. Of note, the type of treatment after first ASCT failure did not significantly influence EFS.

In another analysis, investigators from the Center for International Blood and Marrow Transplant Research (CIBMTR) developed a prognostic model for post-transplant PFS by evaluating risk factors at transplantation and outcomes in 728 adults who underwent ASCT for relapsed/refractory HL [19]. In the model development cohort (n = 337), 4 major adverse risk factors were identified and assigned relative weights for the prognostic scoring system: ≥ 3 chemotherapy regimens (2 points), extranodal involvement (2 points), Karnofsky performance score < 90 (1 point), and chemotherapy resistance (1 point). Based on the total score, 3 risk groups were defined: low risk (total score = 0), intermediate risk (total score = 1-3), and high risk (total score, 4-6). For patients in the low, intermediate, and high risk groups, the 4-year PFS rates were 71%, 60%, and 42%, respectively. The accuracy of the prognostic model was further evaluated and confirmed in the validation cohort (n = 391) and in the entire study population. Therefore, the CIBMTR prognostic model is a useful tool for predicting post-ASCT outcomes based on risk factors available at the time of transplant [19].

Historically, few studies of pre-ASCT prognostic factors have included children, adolescents, and young adults with relapsed/refractory HL. In 2015, Satwani and colleagues described a prognostic model for post-ASCT outcomes in this young patient population [20]. The retrospective analysis included 606

children, adolescents, and young adults (median age, 23 years) who underwent ASCT for relapsed/refractory HL between 1995 and 2010. In this cohort, 4 risk factors present at the time of transplantation significantly predicted worse post-ASCT PFS: Karnofsky/Lansky performance score < 90, time from diagnosis to first relapse of < 1 year, extranodal involvement, and chemoresistant disease. Based on these risk factors, patients were stratified into low-risk, intermediate-risk, and high-risk groups that correlated with 5-year PFS rates of 72%, 53%, and 23%, respectively. By identifying young adults who are at high risk of post-transplant progression, this model may be useful for determining which patients may benefit from novel treatment approaches and/or maintenance regimens following ASCT [20].

Summary

Hodgkin lymphoma has a unique biology with many opportunities for targeted therapy. Initial treatment regimens are potentially curative for many patients, but PFS and OS outcomes differ based on prognostic factors. Many relapsing patients can be salvaged with HDT/ASCT. Post-transplant outcomes are determined by responses to salvage therapy and a range of patient and disease characteristics. Across multiple studies, several adverse prognostic factors present following salvage therapy and/or at the time of transplant have consistently correlated with worse post-ASCT outcomes:

- FDG-PET negativity following salvage chemotherapy
- Receiving multiple treatment regimens prior to ASCT (i.e., chemoresistant disease)
- Poor performance status and/or constitutional symptoms
- Early (< 1 year) relapse following transplant
- Extranodal disease

Novel treatment strategies are being explored to improve the number of complete responses prior to ASCT in relapsed/refractory HL. Patients who relapse following transplant may benefit from treatment with novel therapies that exploit the unique biology in HL.

Targeted Therapy for HL Following Autologous Stem Cell Transplant: Decisions That Can Make a Difference

John Sweetenham, MD, FRCP, FACP

In current practice, ASCT is potentially curative in approximately 50% of patients with relapsed/refractory HL [19, 21-23]. However, treatment success is largely dependent on favorable prognostic factors and the tumor being sensitive to salvage chemotherapy prior to transplant. As discussed in the previous section, adverse prognostic factors such as short first complete response, extranodal involvement, and detectable disease at the time of transplant are associated with worse post-ASCT outcomes [21]. Over the past 20 years of exploring new therapeutic options for patients undergoing ASCT, no significant improvements in FFTF and OS outcomes have been shown in this setting.

Prognosis is especially poor for patients with HL who relapse or demonstrate refractory disease following ASCT. In a study of 756 patients undergoing ASCT for relapsed/refractory HL, the median OS was 2.4 years among those who relapsed following transplantation [24]. At present, allogeneic stem cell transplantation (allo-SCT) appears to be the only option for gaining long-term disease control in patients with HL who progress post-ASCT [25, 26]. In phase II studies of allo-SCT, long-term PFS rates have ranged from 18% to 32% [25, 26]. However, this treatment modality is associated with significant morbidity and high treatment-related mortality. Improving cure rates associated with ASCT is necessary to minimize the need for allo-ASCT in patients with HL.

Potential to Improve Cure Rates for Patients Undergoing ASCT

Post-transplant relapse is a devastating event that should be prevented in patients undergoing ASCT for relapsed/refractory HL. The immediate post-ASCT period provides a critical window of opportunity, when tumor burden is at its lowest, to enhance the cure rate. Therefore, there is an urgent need to treat patients early to eradicate residual lymphoma. In addition, to increase the likelihood of preventing relapse post-ASCT, early consolidation and maintenance regimens should include agents with proven efficacy in HL.

Brentuximab Vedotin

Brentuximab vedotin is an ADC comprised of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E (MMAE). When brentuximab vedotin binds to tumor cells that express the CD30 surface antigen, the ADC-CD30 complex is internalized by endocytosis

and traffics to the lysosome. Following lysosomal degradation and cleavage of the linker, MMAE is released into the cell. The MMAE molecules then bind to tubulin and disrupt the microtubule network, leading to G2/M cell cycle arrest and apoptosis. In 2011, brentuximab vedotin was approved by the Food and Drug Administration (FDA) for the treatment of HL after failure of ASCT, or after failure of 2 or more combination chemotherapy regimens in patients who are not candidates for transplant.

In 2015, Moskowitz and colleagues presented findings from the AETHERA trial, which was the first phase III trial to demonstrate improved PFS with maintenance therapy after ASCT [14]. The prospective, randomized, double-blind trial included 329 patients with HL who were at high risk for residual disease post-transplant based on 1 of 3 eligibility criteria: refractory to frontline treatment, relapsed < 12 months of frontline therapy, or relapsed ≥ 12 months after frontline therapy with extranodal disease.

All patients received salvage therapy of the investigators' choice and were restaged. Those who achieved CR, PR, or stable, non-progressing disease proceeded to ASCT, while those with progressive disease no longer continued in the trial. After completing ASCT, patients were randomly assigned to treatment with best supportive care plus 16 cycles of brentuximab vedotin 1.8 mg/kg every 3 weeks (n = 165) or placebo (n = 164) for up to 1 year. Patients with post-transplant progression in the placebo group were eligible to leave the trial and receive brentuximab vedotin as part of another study. The primary study endpoint was PFS by independent review. Secondary endpoints included OS, safety, and tolerability.

The baseline patient characteristics were similar in the brentuximab vedotin and placebo groups (Table 3). Of note, approximately 60% of patients in both treatment arms were refractory to frontline therapy, and nearly half of patients underwent ≥ 2 prior lines of systemic salvage therapy.

Table 3. Baseline Patient Characteristics in the Phase III AETHERA Trial [14]

	Brentuximab vedotin (n = 165)	Placebo (n = 164)
Median age, years (range)	33 (18 - 71)	32 (18 - 76)
Number of prior lines of systemic salvage therapy		
1	57%	52%
≥ 2	43%	48%
Status after frontline therapy		
Refractory	60%	59%
Relapse < 12 months	32%	33%
Relapse ≥ 12 months	8%	8%
Response to salvage therapy pre-ASCT		
Complete response	37%	38%
Partial response	35%	34%
Stable disease	28%	28%
Extranodal disease at pre-ASCT relapse	33%	32%
B symptoms after frontline therapy	28%	24%
Pre-ASCT PET status		
FDG-positive	39%	31%
FDG-negative	34%	35%
Not available	27%	34%

ASCT, autologous stem cell transplantation.

After a median follow-up of 3 years, PFS results significantly favored treatment with brentuximab vedotin (Table 4). As determined by investigator review, the median PFS was not reached in the brentuximab vedotin group, compared with 15.8 months in the placebo group (HR, 0.517). These findings are consistent with the PFS benefit observed in the brentuximab vedotin group at 2 years. By investigator review, the 2-year PFS was 65% in the brentuximab vedotin group and 45% in the placebo group (HR, 0.50; 95% CI, 0.36-0.70). An independent review of PFS at 2 years showed a similar improvement with brentuximab vedotin compared with placebo (63% versus 51%, respectively; HR, 0.57, 95% CI: 0.40-0.81, P = 0.001).

There was no difference in OS between the brentuximab vedotin and

Table 4. Responses to Brentuximab Vedotin Maintenance Therapy Versus Placebo after ASCT in High-Risk Hodgkin Lymphoma in the Phase III AETHERA Trial [14]

	Brentuximab vedotin (n = 165)	Placebo (n = 164)	HR (95% CI)	P Value
Investigator Review				
Median PFS	Not reached	15.8 months	0.517	NR
2-year PFS	65%	45%	0.50	NR
Independent Review				
Median PFS	43 months	24 months	0.57	.001
2-year PFS	63%	51%	0.57	.001

ASCT = allogeneic stem cell transplantation; HR = hazard ratio; NR = not reported; PFS = progression-free survival.

placebo groups (P = 0.62). However, the OS analysis was confounded by a high crossover rate, with 84% of patients in the placebo group crossing over to brentuximab vedotin maintenance therapy. Furthermore, many patients who were initially assigned to the placebo group received subsequent single-agent chemotherapy (28%), multi-agent chemotherapy (43%), radiation (30%), and/or allo-SCT (30%) at the time of progression. For the overall study population, the 2-year estimated OS was 88%. Survival results in each groups will be reevaluated at the final study analysis in 2020.

The magnitude of PFS benefit with brentuximab vedotin appeared to be greater among patients with high-risk characteristics at the time of transplantation. Patients with a CR or PET-negative disease at the time of ASCT experienced only a modest improvement in PFS with brentuximab vedotin. By comparison, the PFS benefit associated with brentuximab vedotin was higher in the subgroups of patients with CR or PET-negative disease plus ≥ 2 risk factors or extranodal disease at relapse.

Peripheral neuropathy (PN) was the most prevalent toxicity in the trial. In total, 112 of 167 patients (67%) in the brentuximab vedotin reported any grade of PN. Of these, 22 patients reported a maximum grade 3 event. No patients experienced a PN event of grade 4 or higher. Symptoms of PN could include peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, muscular weakness, hypoesthesia, gait disturbance, neuralgia, amyotrophy, decreased vibratory sense, hyporeflexia, peroneal nerve palsy, and sensory disturbance. With additional follow-up, symptoms improved or resolved for 88% of patients. Among 112 patients who reported any PN event during the trial, 38 had ongoing symptoms at the last study assessment. An analysis of quality of life (QoL) demonstrated a gradual decline in QoL scores throughout the duration of the study that was similar in both treatment groups. The presence of PN did not influence overall QoL in either treatment arm.

In summary, based on updated findings and subgroup analyses from the AETHERA trial, brentuximab vedotin has emerged as a potential new standard of care in patients with cHL at high risk of relapse or progression after ASCT. Consolidation treatment with brentuximab vedotin resulted in a sustained PFS benefit relative to placebo approximately 3 years after the last patient was randomized to treatment.

Several factors appeared to influence treatment outcomes. Patients with more risk factors for relapse post-ASCT appeared to have the greatest benefit from consolidation therapy, suggesting that physicians should consider each patient's complete risk factor profile when making treatment decisions. In addition, estimated PFS rates were higher in patients who remained on therapy longer compared with patients who discontinued early. Patients who relapsed in the placebo or brentuximab vedotin consolidation arms and subsequently received (re)treatment with brentuximab vedotin had similar response rates to those previously reported for brentuximab vedotin in the relapsed/refractory setting [27]. The final analysis for overall survival will provide further insights into the role of brentuximab vedotin in providing long-term disease control for patients undergoing ASCT for relapsed/refractory cHL.

PD-1 Pathway Inhibitors

As discussed in the previous section, the pathophysiology of cHL is characterized by rare RS cells surrounded by ineffective immune infiltrating cells, suggesting that these tumors escape immune surveillance [28]. The PD-1 signaling pathway mediates intercellular signals that block T cell activation and attenuate the host antitumor response [29, 30]. The membrane-bound PD-1 receptor ligand PD-L1 is over-expressed on < 85% of RS cells in cHL tumors [31]. Genetic amplification of chromosome 9p24.1 locus and EBV infection, both of which occur frequently in cHL, also correlate with PD-L1 and PD-L2 overexpression [31, 32]. Therefore, multiple mechanisms of PD-1 pathway induction appear active in cHL.

Table 5. Response to Nivolumab in Relapsed/Refractory Hodgkin Lymphoma [4]

	All patients, % (N = 23)
Overall response rate	87%
Complete response	17%
Partial response	70%
Stable disease	13%
PFS at 24 weeks	86%

PFS, progression-free survival.

Nivolumab

Nivolumab is anti-PD-1 monoclonal antibody that blocks anti-PD-1 signaling, potentiates T cell activity, and restores antitumor immunity. In 2015, Ansell and colleagues presented preliminary findings from an ongoing study of nivolumab in patients with relapsed/refractory cHL [4]. At the time of publication, the study enrolled 23 patients with cHL who failed aggressive first-line therapy, including treatment

with brentuximab vedotin (78%) and/or ASCT (78%). All patients received treatment with nivolumab (3 mg/kg) by IV infusion every 2 weeks until disease progression or excessive toxicity. The study objectives were to measure the safety and efficacy of PD-1 inhibition in relapsed/refractory HL.

Treatment with nivolumab demonstrated substantial clinical activity (Table 5). The ORR was 87% and included a CR in 4 patients (17%) and a PR in 16 patients (70%). Three additional patients (13%) achieved stable disease. Furthermore, all patients achieved a reduction in tumor burden in response to nivolumab. At the time of the analysis, 11 patients (48%) had ongoing responses. Among responding patients, 60% of responses occurred in the first 8 weeks of nivolumab treatment. The 24-week PFS was 86%.

Nivolumab had an acceptable safety profile in this heavily pretreated population. The most common drug-related AEs of any grade were rash (22%), decreased platelet count (17%), fatigue (13%), pyrexia (13%), diarrhea (13%), nausea (13%), and pruritus (13%). In total, 5 patients (22%) reported grade 3 AEs, including 1 case each of decreased lymphocyte count, increased lipase level, stomatitis, myelodysplastic syndrome, and pancreatitis. Two patients discontinued treatment due to AEs, and no patients reported grade 4 or 5 drug-related AEs.

In summary, nivolumab shows potent anti-lymphoma activity in relapsed/refractory cHL, decreasing tumor burden in 100% of patients. Based on these findings, the FDA designated nivolumab as a breakthrough therapy for cHL by the FDA. On May 17, 2016, with additional phase II data confirming the high ORR of nivolumab in this treatment setting, the FDA granted accelerated approval of nivolumab in patients with cHL who have relapsed or progressed after ASCT and post-transplantation brentuximab vedotin [33].

Pembrolizumab

Pembrolizumab is a humanized anti-PD-1 monoclonal antibody that is currently approved for the treatment of patients with advanced refractory melanoma and patients with metastatic, refractory, PD-1-positive non-small cell lung cancer (NSCLC). Based on its activity in solid tumors, pembrolizumab is currently under evaluation in a range of hematologic malignancies.

Table 6. KEYNOTE-013: Responses to Pembrolizumab in Relapsed/Refractory Hodgkin Lymphoma [35]

	ASCT failure (n = 23)	ASCT ineligible/refused (n = 9)	All patients (N = 31)
Overall response	73%	44%	65%
Complete response	14%	22%	16%
Partial response	59%	22%	48%
Stable disease	18%	33%	23%
Progressive disease	9%	22%	13%
PFS at 24 weeks	–	–	69%

Abbreviations: ASCT, autologous stem cell transplantation; PFS, progression-free survival.

The KEYNOTE-013 study is an ongoing phase Ib trial of pembrolizumab in patients with relapsed/refractory cHL following brentuximab vedotin failure [34, 35]. At the 2015 ASH annual meeting, KEYNOTE-013 investigators presented findings from an independent expansion cohort of patients with cHL [35]. To enroll in the cHL cohort (N = 31), all patients had to have failed prior treatment with brentuximab. In addition, 71% of patients had failed prior ASCT, while the remaining 29% were transplant ineligible or refused ASCT. All patients received pembrolizumab 10 mg/kg every 2 weeks for up to 2 years or until confirmed PD or unacceptable toxicity. Responses were assessed by CT and PET scans at 12 weeks and then every 8 weeks.

The ORR was 65%, including 5 patients who achieved CR (16%) and 15 patients who achieved PR (48%). In an analysis of best response, 90% of patients had a reduction of ≥50% in their target lesions compared with baseline. Response rates were generally higher for patients who failed ASCT than for those who were transplant ineligible or refused ASCT (Table 6). Among responders, 80% of responses occurred by week 12. Responses were durable, with 71% of patients having a duration of response of at least 24 weeks. The PFS at 24 weeks was 69%.

The most common AEs associated with pembrolizumab were gastrointestinal symptoms, including diarrhea (16%) and nausea (13%). Five patients (16%) developed grade 3 AEs, including 1 case each of elevated liver enzymes, colitis, nephrotic syndrome and back pain, joint swelling, and axillary pain. Two patients discontinued treatment due to grade 2 pneumonitis (n = 1) and grade 3 nephrotic syndrome (n = 1). No grade 4 or 5 AEs were reported.

Overall, initial findings from the KEYNOTE-013 phase Ib trial support the further exploration of pembrolizumab in patients with cHL. The ongoing trial continues to enroll patients with relapsed/refractory cHL and other hematologic malignancies, with a total target enrollment of 222 patients and an estimated study completion date of June 2018 [36].

Other Novel Treatment Approaches

Brentuximab vedotin and PD-1 pathway inhibitors represent two recent examples of shifting standards of care for patients with relapsed/refractory cHL. Multiple novel drug classes also demonstrate promising activity in cHL, including histone deacetylase (HDAC) inhibitors, phosphoinositide-3 kinase (PI3K) signaling pathway inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and immunomodulatory drugs (IMiDs) [37]. Using these agents in combination may result in more effective and less toxic treatment regimens. A phase I study demonstrated the activity of panobinostat plus everolimus in patients with relapsed/refractory HL and non-Hodgkin lymphoma [38]. In the HL group (n = 14), treatment with the HDAC inhibitor and mTOR inhibitor resulted in an ORR of 43%, including a CR of 15%.

Future treatment approaches are likely to incorporate multiple mechanisms of action to maximize the anti-lymphoma effects of treatment. Indeed, the availability of brentuximab vedotin and a PD-1 pathway inhibitor in patients with relapsed/refractory HL has open new avenues for the development of combination regimens in patients with cHL [37]. Emerging examples of combination treatment strategies in cHL include [37]:

- Brentuximab vedotin/ chemotherapy
- Brentuximab vedotin/PD-1 pathway inhibitor
- Brentuximab vedotin/HDAC inhibitor
- Brentuximab vedotin/PI3K or mTOR inhibitor
- Brentuximab vedotin/PD-1 pathway inhibitor/chemotherapy
- Brentuximab vedotin/PD-1 pathway inhibitor/HDAC inhibitor
- Brentuximab vedotin/PD-1 pathway inhibitor/PI3K or mTOR inhibitor

Summary

Consolidation therapy with brentuximab vedotin following ASCT in relapsed/refractory cHL improves PFS with manageable toxicity. In addition, treatment with brentuximab vedotin reduces the number of patients requiring subsequent allo-SCT. The role of consolidation therapy for patients who are in radiologic or metabolic CR at the time of ASCT requires further investigation. After failing treatment with brentuximab vedotin, the PD-1 signaling pathway inhibitors provide additional options for salvage therapy. As additional agents demonstrate activity in relapsed/refractory cHL, brentuximab vedotin is likely to form the backbone for future strategies of novel combinations in the post-transplant setting.

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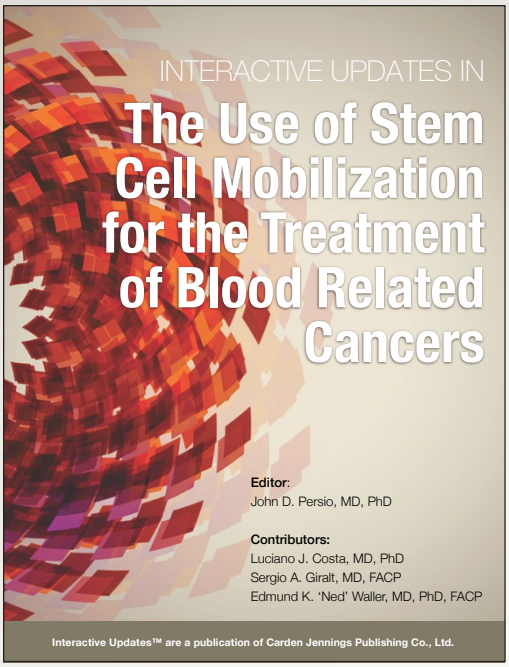

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1. **Should all patients presenting with advanced stage HL (stage IIIB) receive PET/CT prior to initiation of systemic therapy?**
   A. Yes
   B. No

2. **In a patient with stage IIB NSHL that achieved a PR after 2-3 cycles of chemotherapy, would your routinely consider a PET/CT?**
   A. Yes
   B. No
   C. Uncertain

3. **A HL patients who relapsed following transplant, new novel targeted agents have demonstrated a doubling of OS**
   A. Yes
   B. No

4. **In a patient with relapse/refractory HL, all of the following prognostic factors are predictors of post-transplant relapsed except the following:**
   A. Performance status
   B. Extra nodal involvement
   C. Elevated LDH
   D. Chemosensitivity
   E. Time from diagnosis to first relapse <1 year