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Managing Risk in Hodgkin Lymphoma

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Abstract: Approximately 90% of patients with limited-stage Hodgkin lymphoma are cured. The cure rate in advanced-stage Hodgkin lymphoma is dramatically better than it once was, but it is still lower than the rate in patients with limited disease. The choice of treatment is based on several factors, including symptoms, disease stage, extent of tumor burden, and prognosis. Positron emission tomography scanning can be used to assess the patient's stage of disease, which can allow further individualization of therapy. Traditional frontline treatment options include doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and, for high-risk patients, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). Autologous stem cell transplantation cures approximately 50% of patients. The antibody-drug conjugate brentuximab vedotin is very active in relapsed/refractory Hodgkin lymphoma. Data presented at the 2014 meeting of the American Society of Hematology (ASH) showed that brentuximab vedotin was beneficial in several settings, including as consolidation therapy post-transplant in patients at high risk for relapse, as first-line salvage therapy in relapsed/refractory Hodgkin lymphoma prior to autologous hematopoietic cell transplantation, and in combination with bendamustine in relapsed/refractory disease. The ASH meeting also offered promising data on novel agents, such as the programmed cell death 1 (PD-1) inhibitors. In this monograph, 4 experts in the management of Hodgkin lymphoma discuss various aspects of the disease and provide their perspectives on the new data presented at the ASH meeting.

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Frontline Management of Hodgkin Lymphoma Patients With High-Risk Disease

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Like most lymphomas, Hodgkin lymphoma is a B-cell malignancy. The incidence of Hodgkin lymphoma has remained relatively stable over the past 2 decades.[1] Hodgkin lymphoma has 2 histologic subtypes: classical (occurring in approximately 95%) and nodular lymphocyte-predominant (occurring in approximately 5%).[2] Classical Hodgkin lymphoma has a variety of appearances under the microscope; in the United States, nodular sclerosis is the most common appearance, whereas mixed cellularity is more common in developing countries. Two other less-common types of classical Hodgkin lymphoma are lymphocyte depleted and lymphocyte predominant. Nodular lymphocyte-predominant Hodgkin lymphoma has consistent high CD-20 expression. It has a more chronic course than classical Hodgkin lymphoma, but many physicians use the same treatment approach for both.

Patients with Hodgkin lymphoma are classified according to their extent of disease based on the Ann Arbor Staging System, which was devised in 1971 (Table 1).[3] Prognosis will vary according to the patient's stage. Stages 1 and 2 are considered limited-stage disease. These patients are often subdivided based on the presence of high-risk features—such as a very high erythrocyte sedimentation rate, systemic symptoms, multiple sites of disease, male sex, and a low lymphocyte count. The categorization of high-risk and low-risk disease varies; several different definitions have been used in clinical trials and at various institutions.[4]

Hodgkin lymphoma can present with unusual characteristics. For example, patients can become intolerant to alcohol ingestion and experience pain at the site of the disease, or develop a fever that persists for several days, and then resolves and returns (a phenomenon known as Pel-Ebstein fever).

Table 1. Ann Arbor Staging System

Stage 1: Lymph node involvement in 1 place
Stage 2: Lymph node involvement in more than 1 place, but on 1 side of the diaphragm
Stage 3: Lymph nodes on both sides of the diaphragm are involved
Stage 4: Disease involves other organs, such as the lung or the liver

Data from Carbone P et al. *Cancer Res.* 1971;31:1860-1861.[3]

There is a bimodal distribution of Hodgkin lymphoma, with one peak at a median age of 25 to 30 years and another peak in people older than 60 years.[5] Although Hodgkin lymphoma manifests in a similar manner regardless of age, in the past, it had been suggested that younger and older patients were experiencing a different disease because treatment was far more effective in younger patients than older patients. Hodgkin lymphoma patients ages 50 to 60 years or older are less likely than younger patients to survive, even with equal disease characteristics.

History of Hodgkin Lymphoma

In 1832, Thomas Hodgkin, MD, wrote a paper describing 7 patients who died with massive lymphadenopathy.[6]

He was not the first person to describe such patients, but his name was given to the disease in an article published in 1877 by Samuel Wilks, MD.[7]

Approximately 25 years later, Dorothy Reed, a medical student at Johns Hopkins, and Carl Sternberg, an Austrian pathologist, independently described a multinuclear giant cell associated with enlarged lymph nodes.[8,9] This discovery led to the recognition that Hodgkin disease differed from other types of lymphoma. The presence of the Reed-Sternberg cell is now a key part of the diagnosis of Hodgkin lymphoma.

Frontline Treatment of Hodgkin Lymphoma

Treatments have improved dramatically in the past few decades. Initially, treatment involved radiotherapy, which was first used early in the 20th century.[10-12] By 1958, it was clear that radiotherapy improved outcome and could even cure some patients.[11] In the late 1950s, linear accelerators were discovered, improving the safety and effectiveness of radiotherapy.[13] In the early 1970s, an understanding of the concept of disease staging led to the development of the Ann Arbor Staging System and various histologic classification systems.[3]

The choice of treatment is based on several factors, including symptoms, disease stage, extent of tumor burden, and prognosis. Positron emission tomography (PET) scanning can be used to assess the patient's stage of disease, which can allow further individualization of therapy. A negative PET scan after treatment is the best indicator of a durable remission.[4]

Need for Better Treatments

As research progressed, it became apparent that most of the patients who were cured with radiotherapy had early-stage disease.[10-12] For advanced-stage Hodgkin lymphoma, achieving a cure with radiotherapy alone was difficult and unlikely. In the 1960s, Dr Vincent DeVita and colleagues at the National Cancer Institute developed a regimen consisting of mechlorethamine, vincristine, methotrexate, and prednisone (MOMP). Procarbazine was later substituted for methotrexate, and the regimen became known as MOPP.[14] In 1970, DeVita and colleagues reported that patients with advanced-stage Hodgkin lymphoma could sometimes be cured with drugs alone.[15]

Radiotherapy had improved survival—that is, patients lived longer with the disease. However, the death rate in Hodgkin lymphoma did not fall significantly until chemotherapy was added to the treatment plan. Management approaches began to incorporate chemotherapy into treatment at all stages of the disease, and today, chemotherapy—sometimes followed by radiotherapy—is the standard.

Treatment in the Modern Era

Approximately 90% of patients with limited-stage Hodgkin lymphoma are cured.[4] For these patients, a debate has centered on how to minimize the necessary treatment while still maintaining a high cure rate. The best-prognosis patients have been more likely to die of the consequences of therapy than of the lymphoma.[4]

The cure rate in advanced-stage Hodgkin lymphoma is dramatically better than it once was, but it is still lower than the rate in patients with limited disease. In the 1980s, research at my institution and others showed that autologous stem cell transplantation (ASCT) can cure some Hodgkin lymphoma patients in whom standard therapy fails.[16] This approach is still the standard for most patients in whom upfront treatment fails.

ABVD vs BEACOPP

In 1975, Dr Gianni Bonadonna and colleagues described a regimen consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). This regimen is the most commonly used following studies that showed a superior outcome when it was compared with MOPP.[17] More recently, the German Hodgkin Study Group developed a regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), first in lower doses and then in a more intense regimen known as escalated BEACOPP, the more common form used today.[18] Currently, standard therapy for advanced-stage Hodgkin lymphoma is either ABVD or escalated BEACOPP, depending upon the patient's characteristics and the physician's preferred approach. The 12-week Stanford V regimen is also an effective combination of chemotherapy and radiotherapy, but it is less commonly used than ABVD.[19]

Today, the debate is between ABVD vs BEACOPP for advanced-stage Hodgkin lymphoma. BEACOPP is much more intensive and has a toxicity profile that includes infertility and a higher mortality. It is not usually administered to patients with early-stage disease or those with a good prognosis. In a study from Italy in advanced-stage Hodgkin lymphoma, more patients were cured with escalated BEACOPP than ABVD.[20] However, when patients who failed ABVD went on to transplant, there was no significant difference between the groups in survival. The debate therefore centers on whether it is preferable to give BEACOPP, which has a higher cure rate but more toxicity, or ABVD, which might achieve a similar cure rate when followed by transplantation in patients who fail initial treatment. In the United States, most physicians treat with ABVD and then transplant the patients who are not cured. Even so, this is an open question, and patients at very high risk might do better with escalated BEACOPP.

New Management Approaches

Brentuximab vedotin, the antibody drug conjugate, was approved in 2011 for Hodgkin lymphoma patients who have failed ASCT or who are not candidates for ASCT and have failed at least 2 multiagent chemotherapy regimens.[21] It is very active in relapsed/refractory Hodgkin lymphoma, with an overall response rate of 75% and a complete remission rate of 34% in a pivotal, phase 2 trial.[22] Research is underway to determine how brentuximab vedotin might fit into the treatment armamentarium. In a phase 2 trial of heavily pretreated patients, the response rate among evaluable patients was 56%, with a median duration of response of 5 months.[23] Although brentuximab vedotin is not associated with a high cure rate, it is very active and can allow patients with relapsed/refractory disease to proceed to transplantation. The success with brentuximab vedotin in relapsed/refractory patients has led to research in the frontline setting. Brentuximab vedotin was combined with ABVD or AVD (without the bleomycin) in a phase 1, dose-escalation trial.[24] The complete remission rate was 95% in patients who received brentuximab vedotin plus ABVD and 96% in patients who received it with AVD. The study showed that the interaction with bleomycin was associated with mortality from pulmonary disease. The ongoing phase 3 ECHELON-1 (A Randomized, Open-Label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma) trial is evaluating brentuximab vedotin in combination with AVD vs ABVD alone.[25,26] This study is currently recruiting participants. The results will be important to the management of patients with Hodgkin lymphoma.

Sequential therapy was examined in a pilot phase 2 study presented at the 2014 American Society of Hematology (ASH) meeting. The study enrolled 12 patients with untreated Hodgkin lymphoma, and treatment consisted of brentuximab vedotin followed by ABVD, with or without radiotherapy. The complete response rate was 83%, and toxicity was limited (Table 2).[27]

Several presentations at the 2014 ASH meeting focused on brentuximab vedotin in the relapsed/refractory setting. Clinical trial data showed that brentuximab vedotin was beneficial both before transplantation[28] and as consolidation therapy after transplantation.[29]

Another area of research is inhibition of the programmed cell death 1 (PD-1) protein, which is expressed on the surface of activated T cells.[30] PD-L1 and PD-L2, the ligands to PD-1, are overexpressed on certain tumor cells and macrophages in the tumor microenvironment. Recent data presented at the ASH meeting suggest that PD-1 inhibitors, by not allowing inactivation of the T cells, will likely impact management in patients with relapsed/refractory Hodgkin lymphoma.[31-34] One study, which included many patients in whom brentuximab vedotin had failed, found a response rate of 87% and a 24-week progression-free survival of 86%.[33]

Table 2. Toxicities in a Pilot Phase 2 Trial of Brentuximab Vedotin Followed by ABVD

	Grade 1/2 n (%)	Grade 3 n (%)
Hepatic	0	2 (17)
Gastrointestinal	11 (92)	0
Dermatologic	5 (42)	0
Pyrexia	3 (25)	0
Anemia	2 (17)	0
Infusion reaction	1 (8)	0
Other	8 (67)	0

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

Data from Zinzani PL et al. Brentuximab vedotin followed by ABVD in patients with previously untreated Hodgkin Lymphoma. A pilot phase II study [ASH abstract 3088]. *Blood*. 2014;124(suppl 21).[27]

Disclosure

Dr Armitage has disclosed consulting relationships with Celgene, GlaxoSmithKline, Roche, Spectrum, and Ziopharm. He is a member of the Board of Directors of Tesaro Inc.

References

1. SEER State Fact Sheets: Hodgkin Lymphoma. Surveillance, Epidemiology, and End Results Program. http://seer.cancer.gov/statfacts/html/hodg.html. Accessed December 22, 2014.
2. Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2008.
3. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res*. 1971;31:1860-1861.
4. Armitage JO. Early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363(7):653-662.
5. Ficalora RD, Mueller PS, Beckman TJ, Beliveau M, eds. *Mayo Clinic Internal Medicine Board Review*. 10th ed. New York, New York: Oxford University Press; 2013:530.
6. Hodgkin T. On some morbid appearances of the absorbent glands and spleen. *Med Chir Trans*. 1832;17:68-114.
7. Wilks S. Historical notes on Bright's, Addison's and Hodgkin's disease. *Guy's Hosp Rep*. 1877;22:259-274.
8. Reed D. On the pathological changes in Hodgkin's disease, with special reference to its relation to tuberculosis. *Johns Hopkins Hosp Rep*. 1902;10:133-196.
9. Sternberg C. Uber eine eigenartige unter dem Bilde der Pseudoleukamie verlaufende Tuberculose des lymphatischen Apparates. *Ztschr Heilk*. 1898;19:21-90.
10. Easson EC, Russell MH. Cure of Hodgkin's disease. *Br Med J*. 1963;1:1704-1707.
11. Peters MV, Middlemiss KC. A study of Hodgkin's disease treated by irradiation. *Am J Roentgenol Radium Ther Nucl Med*. 1958;79:114-121.
12. Kaplan HS. The radical radiotherapy of regionally localized Hodgkin's disease. *Radiology*. 1962;78:553-561.
13. Ginzton EL, Mallory KB, Kaplan HS. The Stanford medical linear accelerator. I. Design and development. *Stanford Med Bull*. 1957;15(3):123-140.
14. DeVita VT, Hubbard SM, Longo DL. The chemotherapy of lymphoma: looking back, moving forward—the Richard and Hinda Rosenthal Foundation Award Lecture. *Cancer Res*. 1987;47:5810-5824.
15. Devita VT Jr, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med*. 1970;73:881-895.
16. Kessinger A, Armitage JO, Smith DM, Landmark JD, Bierman PJ, Weisenburger DD. High-dose therapy and autologous peripheral blood stem cell transplantation for patients with lymphoma. *Blood*. 1989;74(4):1260-1265.

17. 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(1):252-259.
18. von Tresckow B, Plütschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol*. 2012;30:907-913.
19. Bartlett NL, Rosenberg SA, Hoppe RT, et al. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. *J Clin Oncol*. 1995;13(5):1080-1088.
20. 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(3):203-212.
21. FDA approves Adcetris to treat two types of lymphoma. US Food and Drug Administration. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268781.htm. Posted August 19, 2011. Accessed December 18, 2014.
22. 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(18):2183-2189.
23. Moskowitz AJ, Hamlin PA Jr, Perales MA, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2013;31(4):456-460.
24. Younes A, Connors JM, Park SI, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. *Lancet Oncol*. 2013;14(13):1348-1356.
25. Ansell SM, Younes A, Connor JM, et al. Phase 3 study of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as front-line treatment for advanced classical Hodgkin lymphoma (HL): ECHELON-1 study [ASCO abstract TPS8613]. *J Clin Oncol*. 2014;32:5(suppl).
26. ClinicalTrials.gov. Phase 3 frontline therapy trial in patients with advanced classical Hodgkin lymphoma. https://clinicaltrials.gov/ct2/show/NCT01712490. Identifier: NCT01712490. Accessed December 24, 2014.
27. Zinzani PL, Luminari S, Merli F, et al. Brentuximab vedotin followed by ABVD in patients with previously untreated Hodgkin lymphoma. A pilot phase II study [ASH abstract 3088]. *Blood*. 2014;124(suppl 21).
28. Chen RW, Palmer J, Martin P, et al. Results of a phase II trial of brentuximab vedotin as first line salvage therapy in relapsed/refractory HL prior to AHCT [ASH abstract 501]. *Blood*. 2014;124(suppl 21).
29. Moskowitz CH, Nadamanee A, Masszi T, et al. The AETHERA trial: results of a randomized, double-blind, placebo-controlled phase 3 study of brentuximab vedotin in the treatment of patients at risk of progression following autologous stem cell transplant for Hodgkin lymphoma [ASH abstract 673]. *Blood*. 2014;124(suppl 21).
30. Wang C, Thudium KB, Han M, et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. *Cancer Immunol Res*. 2014;2(9):846-856.
31. Armand P, Ansell SM, Lesokhin AM, et al. Nivolumab in patients with relapsed or refractory Hodgkin lymphoma - preliminary safety, efficacy and biomarker results of a phase I study [ASH abstract 280]. *Blood*. 2014;124(suppl 21).
32. Lesokhin AM, Ansell SM, Armand P, et al. Preliminary results of a phase I study of nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies [ASH abstract 291]. *Blood*. 2014;124(suppl 21).
33. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma [published online December 6, 2014]. *N Engl J Med*. doi:10.1056/NEJMoa1411087.
34. Moskowitz CH, Ribrag V, Michot J-M, et al. PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results from a phase 1b study (KEYNOTE-013) [ASH abstract 290]. *Blood*. 2014;124(suppl 21).

Treatment of Relapsed/Refractory Hodgkin Lymphoma

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Management of Patients Refractory to ABVD

The standard frontline treatment for Hodgkin lymphoma consists of ABVD. Among patients with advanced-stage disease, up to 10% will not achieve a complete remission with frontline therapy, and 20% to 30% of patients who do respond will subsequently relapse.[1,2] The current standard of care for relapsed/refractory Hodgkin lymphoma patients is 2 to 3 cycles of a combination chemotherapy regimen that is stronger than ABVD—such as ifosfamide, carboplatin, and etoposide (ICE); dexamethasone, cisplatin, and cytarabine (DHAP); or gemcitabine, cisplatin, and dexamethasone—to achieve a complete response or partial response before consolidation with ASCT. These combination chemotherapy regimens are usually administered in the inpatient setting. Although the overall response rates range from 62% to 88%, the highest complete response rate was only 26% in the pre-PET era.[3-6] These combination regimens are associated with significant toxicity, most commonly myelosuppression, which can lead to febrile neutropenia, anemia, and thrombocytopenia.[2] Infections are frequent. Patients often require growth factor support, as well as packed red blood cells and/or platelet transfusions. Another concern with this approach is that intensive treatment with chemotherapy can interfere with the ability to obtain sufficient stem cells for ASCT. After treatment with these chemotherapy regimens, the stem cell failure rate reached 15% in the pre-plerixafor era.[3-6]

For Hodgkin lymphoma patients, ASCT is preferred over allogeneic transplantation, based on its increased safety. The typical mortality rate for ASCT can reach 4%,[7,8] compared with 13% to 15% for allogeneic transplantation.[9,10] The use of ASCT has been reported in 2 phase 3 randomized controlled trials.[11,12] In a study from the German Hodgkin's Lymphoma Study Group/European Bone Marrow Transplant Registry, 161 patients with relapsed Hodgkin lymphoma received either 2 cycles of chemotherapy followed by ASCT or 4 cycles of chemotherapy. The ASCT arm had better freedom-from-treatment-failure after 3 years (55% vs 35%; *P*=.02).[12] The results of this study led to the general use of transplantation in patients with relapsed/refractory Hodgkin lymphoma.

Approximately half of patients will not be cured by ASCT.[13] Patients most likely to benefit from ASCT are those who achieved a complete remission (assessed by PET) from the last salvage chemotherapy before transplantation. In a study by Devillier and colleagues, patients who achieved a complete response had a 5-year PFS of 79% and a 5-year overall survival of 90%, compared with 23% and 55%, respectively, among patients who did not achieve a complete response.[14]

Emerging Use of Brentuximab Vedotin Prior to Transplantation

Brentuximab vedotin is an antibody-drug conjugate that consists of 3 components: an antibody to CD30, the antimicrotubule agent monomethyl auristatin E (MMAE), and a protease-cleavable linker that covalently links these components together. Hodgkin lymphoma expresses CD30 on the cell surface. Brentuximab vedotin binds to the CD30, and then the entire conjugate is internalized into the Hodgkin lymphoma cells. Lysosomal enzymes cleave the linker and release MMAE, the cytotoxic component. The MMAE then disrupts the microtubules and causes cell cycle apoptosis. A pivotal phase 2 trial of single-agent brentuximab vedotin was performed in Hodgkin lymphoma patients who had failed ASCT.[15] These patients had initially received treatment with ABVD. After treatment failure, they received ICE salvage therapy followed by transplantation, which also eventually failed. This study showed impressive results for single-agent brentuximab vedotin, with an overall response rate of 75% and a complete response rate of 34%.

Because brentuximab vedotin is a targeted therapy, the toxicity profile is minimal. Few patients developed anemia, thrombocytopenia, or neutropenia.[15] The main adverse event was grade 1 or 2 peripheral neuropathy—in particular, sensory neuropathy. Patients experienced some numbness and a tingling sensation in the fingers and toes. Based on this study, the US Food and Drug Administration granted accelerated approval of brentuximab vedotin for patients with Hodgkin lymphoma who have failed stem cell transplantation.[16] Brentuximab vedotin is the only drug to be approved for Hodgkin lymphoma in the past 20 years, so it has changed the treatment landscape for these patients.

The feasibility of administering single-agent brentuximab vedotin before ASCT in Hodgkin lymphoma patients who have failed frontline therapy, such as ABVD, was examined recently in a phase 2 trial, with preliminary results presented by Dr Alison Moskowitz and colleagues at the 2013 ASH meeting.[17] The aim of this phase 2 trial was to determine whether single-agent brentuximab vedotin would be beneficial before stem cell transplantation in patients who failed frontline therapy, such as ABVD. The standard dosing for brentuximab vedotin is 1.8 mg/kg given intravenously every 3 weeks, which is considered 1 cycle. The study by Dr Moskowitz used a lower dose given more frequently: 1.2 mg/kg was administered weekly for a 3-week period, which was considered 1 cycle. Patients received 2 cycles of treatment and underwent a PET/computed tomography (CT) scan, which showed a complete response in 12 patients (29%). Eleven of these patients proceeded straight to transplantation. Thirty patients (71%) did not attain a complete response after brentuximab vedotin and went on to receive 2 cycles of augmented ICE. Among these patients, 21 (70%) achieved a complete response and proceeded to ASCT, 8 received further treatment, and 1 was lost to follow-up. After transplantation, 92% of patients remained progression-free at a median follow-up of 10 months. Although longer follow-up is needed, this trial showed that there are patients who can undergo transplantation without first receiving ICE chemotherapy.

Data Presented at the 2014 ASH Meeting

The ASH 2014 meeting included several exciting trials in relapsed/refractory Hodgkin lymphoma. I presented results of a phase 2 trial of brentuximab vedotin as first-line salvage therapy in relapsed/refractory Hodgkin lymphoma prior to autologous hematopoietic cell transplantation.[18] This trial evaluated the use of single-agent brentuximab vedotin as salvage chemotherapy in relapsed/refractory Hodgkin lymphoma patients (nearly all of whom failed ABVD) before transplantation. This study used the standard dosage of brentuximab vedotin: 1.8 mg/kg every 3 weeks. After 2 cycles of therapy, patients underwent a PET/CT scan to evaluate for response. Patients who achieved a complete response, a partial response, or stable disease received 2 more cycles of brentuximab vedotin, for a maximum of 4 cycles. (Patients who developed progressive disease were taken off the study.) After 4 cycles of brentuximab vedotin, patients

Table 3. Response in a Phase 2 Trial of Brentuximab Vedotin as First-Line Salvage Therapy in Relapsed/Refractory Hodgkin Lymphoma

	Best Response (%)	Best Response at Cycle 2 (%)	Response at Cycle 4 or End of Treatment (%)
Overall response	69	67	61
Complete response	36	36	36
Partial response	33	31	25
Stable disease	28	31	27
Progressive disease	3	3	11

Data from Chen RW et al. Results of a phase II trial of brentuximab vedotin as first line salvage therapy in relapsed/refractory HL prior to AHCT [ASH abstract 501]. *Blood*. 2014;124(suppl 21).[18]

who achieved a complete response proceeded straight to transplantation. Patients who achieved a partial response had the option of either going straight to transplantation—if their amount of disease was small—or receiving another therapy, such as ICE or DHAP. In our trial, we did not specify whether patients would receive ICE or not, in contrast to the trial by Dr Alison Moskowitz, in which all patients who achieved a partial response received ICE before transplantation. Our approach reflects the fact that different kinds of chemotherapy are used in clinical practice.

Our results were similar to those reported by Dr Moskowitz. Among patients who received brentuximab vedotin alone, the complete response rate was 36%, and the overall response rate was 69% (Table 3). Approximately half of our patients proceeded to transplantation without needing any additional salvage chemotherapy. The remaining patients received additional chemotherapy, such as ICE, before transplantation. At the time of transplantation, 73% of the patients were in complete remission. Our trial showed that brentuximab vedotin was associated with a high response rate and minimal toxicity. No patients in our trial required transfusion or growth factor support, which is needed in approximately 60% of patients who received the ICE chemotherapy regimen. Patients who did not achieve a complete response after the first restaging are continuing in an amended version of this study that is evaluating a dose-augmented regimen of brentuximab vedotin.[19]

Our trial did not show that brentuximab vedotin was better than ICE in terms of efficacy, but it was not designed to do so. The study was designed to show that brentuximab vedotin can be considered an option for first-line salvage therapy. In the study, brentuximab vedotin was much less toxic than ICE while achieving a high overall response rate. An additional benefit to brentuximab vedotin concerns its administration; with standard dosing, it is given in the outpatient clinic once every 3 weeks. Patients who receive treatment with ICE chemotherapy are usually admitted to the hospital for 3 days.

Another study presented at the 2014 ASH meeting evaluated brentuximab vedotin in combination with bendamustine in relapsed/refractory Hodgkin lymphoma.[20]

Table 4. Response in a Trial of Brentuximab Vedotin Plus Bendamustine

	n (%)
Best clinical response*	
Complete remission	40 (83)
Partial remission	6 (13)
Stable disease	1 (2)
Progressive disease	1 (2)
Objective response rate	46 (96)

*Before autologous stem cell transplantation.

Data from LaCasce A et al. Brentuximab vedotin in combination with bendamustine for patients with Hodgkin lymphoma who are relapsed or refractory after frontline therapy [ASH abstract 293]. *Blood*. 2014;124(suppl 21).[20]

Bendamustine is an alkylating agent used to treat other types of lymphomas, such as follicular lymphoma, mantle cell lymphoma, and diffuse large B-cell lymphoma. The patients in this study had relapsed or refractory disease after upfront therapy with ABVD. The response rate was high, at 96%, which included a complete response rate of 83% (Table 4). The adverse events were manageable (premedication was given for infusion-related reactions).

Also at the ASH 2014 meeting, Dr Craig Moskowitz presented data from the pivotal AETHERA (A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant) study.[21] This large, randomized phase 3 trial enrolled high-risk Hodgkin lymphoma patients who underwent transplantation and were then randomized to receive brentuximab vedotin consolidation therapy or placebo. The brentuximab vedotin schedule was 1.8 mg/kg every 3 weeks for up to 16 treatment cycles, which equals nearly a year of treatment. The aim of this trial was to increase the 2-year PFS of the patients who received brentuximab vedotin as consolidation therapy. The study showed that the patients who received brentuximab vedotin had much better outcomes than the patients who did not. At 2 years, the PFS rate by independent review was 63% in the brentuximab vedotin arm vs 51% in the placebo arm.

Another important trial presented at the 2014 ASH meeting was the Southwest Oncology Group (SWOG) study evaluating tandem transplantation (which refers to 2 ASCTs performed back-to-back). For high-risk Hodgkin lymphoma patients who fail ABVD or relapse very quickly, standard care typically involves salvage chemotherapy followed by transplantation. In the SWOG trial, this patient population underwent tandem ASCT.[22] At 5 years, PFS was 55% and overall survival was 84%. Among the 89 patients assessed for toxicities, 70 experienced a grade 4 adverse event (most of which were hematologic).

Challenges in the Management of Patients Refractory to Frontline Chemotherapy

Patients whose disease is refractory to frontline chemotherapy have a much lower rate of cure. In these patients, the goal is to administer therapy that will lead to a complete response before stem cell transplantation. In the past, this approach could be problematic because the amount of chemotherapy needed to achieve a complete response could damage the patient's stem cells or organs, thereby decreasing the chance that the stem cell transplantation would be effective. By itself, transplantation is a harsh procedure, and patients who undergo it should be in good condition.

As a targeted agent, brentuximab vedotin is an ideal therapy before transplantation. It can allow some patients to proceed to transplantation with a complete response and no organ toxicity. Brentuximab vedotin plus 2 cycles of chemotherapy can replace 4 or 5 cycles of chemotherapy.

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References

1. Kuruvilla J. Standard therapy of advanced Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program*. 2009:497-506.
2. Kuruvilla J, Keating A, Crump M. How I treat relapsed and refractory Hodgkin lymphoma. *Blood*. 2011;117(16):4208-4217.
3. Josting A, Rudolph C, Mapara M, et al. Cologne high-dose sequential chemotherapy in relapsed and refractory Hodgkin lymphoma: results of a large multicenter study of the German Hodgkin Lymphoma Study Group (GHSG). *Ann Oncol*. 2005;16(1):116-123.
4. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. *Blood*. 2001;97(3):616-623.
5. Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol*. 2007;18(6):1071-1079.
6. Kuruvilla J, Nagy T, Pintilie M, Tsang R, Keating A, Crump M. Similar response rates and superior early progression-free survival with gemcitabine, dexamethasone, and cisplatin salvage therapy compared with carmustine, etoposide, cytarabine, and melphalan salvage therapy prior to autologous stem cell transplantation for recurrent or refractory Hodgkin lymphoma. *Cancer*. 2006;106(2):353-360.
7. Crump M, Smith AM, Brandwein J, et al. High-dose etoposide and melphalan, and autologous bone marrow transplantation for patients with advanced Hodgkin's disease: importance of disease status at transplant. *J Clin Oncol*. 1993;11(4):704-711.
8. Stewart DA, Guo D, Glück S, et al. Double high-dose therapy for Hodgkin's disease with dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP) prior to high-dose melphalan and autologous stem cell transplantation. *Bone Marrow Transplant*. 2000;26(4)383-388.
9. Anderlini P, Saliba R, Acholonu S, et al. Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in relapsed and refractory Hodgkin's lymphoma: the updated M.D. Anderson Cancer Center experience. *Haematologica*. 2008;93(2):257-264.
10. Chen R, Palmer JM, Popplewell L, et al. Reduced intensity allogeneic hematopoietic cell transplantation can induce durable remission in heavily pretreated relapsed Hodgkin lymphoma. *Ann Hematol*. 2011;90(7):803-808.
11. Linch DC, Winfeld D, Goldstone AH. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993;341(8852):1051-1054.
12. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359:2065-2071.
13. Sureda A, Constans M, Iriondo A, et al; Grupo Español de Linfomas/Trasplante Autólogo de Médula Osea Cooperative Group. *Ann Oncol*. 2005;16(4):625-633.
14. Devillier R, Coso D, Castagna L, et al. Positron emission tomography response at the time of autologous stem cell transplantation predicts outcome of patients with relapsed and/or refractory Hodgkin's lymphoma responding to prior salvage therapy. *Haematologica*. 2012;97(7):1073-1079.
15. 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(18):2183-2189.
16. FDA approves Adcetris to treat two types of lymphoma. US Food and Drug Administration. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268781.htm. Posted August 19, 2011. Accessed December 18, 2014.
17. Moskowitz A, Heiko H, Gerecitano JF, et al. FDG-PET adapted sequential therapy with brentuximab vedotin and augmented ICE followed by autologous stem cell transplant for relapsed and refractory Hodgkin lymphoma [ASH abstract 2099]. *Blood*. 2013;122(21 suppl).
18. Chen RW, Palmer J, Martin P, et al. Results of a phase II trial of brentuximab vedotin as first line salvage therapy in relapsed/refractory HL prior to AHCT [ASH abstract 501]. *Blood*. 2014;124(suppl 21).
19. ClinicalTrials.gov. Brentuximab vedotin before autologous stem cell transplant in treating patients with Hodgkin lymphoma. https://clinicaltrials.gov/ct2/show/NCT01393717?term=brentuximab+vedotin+AND+chen&rank=3. Identifier: NCT01393717. Accessed January 5, 2014.
20. LaCasce A, Bociek RG, Matous J, et al. Brentuximab vedotin in combination with bendamustine for patients with Hodgkin lymphoma who are relapsed or refractory after frontline therapy [ASH abstract 293]. *Blood*. 2014;124(suppl 21).
21. Moskowitz CH, Nadamanee A, Masszi T, et al. The AETHERA trial: results of a randomized, double-blind, placebo-controlled phase 3 study of brentuximab vedotin in the treatment of patients at risk of progression following autologous stem cell transplant for Hodgkin lymphoma [ASH abstract 673]. *Blood*. 2014;124(suppl 21).
22. Smith EP, Li H, Friedberg JW, et al. SWOG S0410/BMT CTN 0703: a phase II trial of tandem autologous stem cell transplantation (AHCT) for patients with primary progressive or recurrent Hodgkin lymphoma (HL) (ClinicalTrials.gov Identifier: NCT00233987) [ASH abstract 676]. *Blood*. 2014;124(suppl 21).

New Frontiers in the Management of Hodgkin Lymphoma

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The central question in Hodgkin lymphoma is whether all patients can be cured. Hodgkin lymphoma patients are divided into 5 risk groups: favorable early stage; unfavorable early stage; unfavorable early stage with tumor bulk; good risk, advanced stage; and poor risk, advanced stage. The most common subtypes are unfavorable early-stage disease (with or without tumor bulk), which occurs in approximately 40% of patients, and favorable advanced-stage disease, which occurs in approximately one-third of patients. The primary treatment is selected based upon these risk groups.

Radiation remains the single most effective "single agent" treatment for Hodgkin lymphoma, but its role continues to diminish. PET imaging is a component of management in untreated patients and in the pretransplant setting. Brentuximab vedotin can be used in various aspects of Hodgkin lymphoma management. Checkpoint inhibitors are an emerging treatment, and their role in the treatment armamentarium will likely evolve throughout the next few years. This article will examine the latest treatment strategies in relapsed/refractory Hodgkin lymphoma, with a focus on data presented at the 2014 ASH meeting.

Relapsed/Refractory Disease

Approximately 9200 cases of Hodgkin lymphoma were reported to the Surveillance, Epidemiology, and End Results Program registry in 2014.[1] Even with optimal treatment, approximately 1600 of these patients will require second-line therapy. Although cure is still the goal for all patients, clinical research has moved in the direction of maintaining the current cure rate while decreasing long-term side effects.

There are several questions regarding the management of relapsed/refractory Hodgkin lymphoma. The RAPID (Response-Adapted PET Trial in Early-Stage Hodgkin's Disease) study enrolled early-stage patients treated with chemotherapy alone.[2] All patients received ABVD for 3 cycles and then underwent restaging based on an interim PET scan. Patients with a negative PET scan received involved-field radiation therapy or no further treatment. Patients with a positive result received treatment with an additional ABVD cycle followed by involved-field radiation therapy. Interim data showed that 74.6% of patients had a negative result after 3 courses. After a median of 34.1 months, 92.6% of patients were progression-free, 5.7% had progressed, and 1.4% had died. The combined 3-year progression-free survival was 92.2%, and overall survival was 98.2%. There are unclear implications for salvage options in patients who receive only 3 months of chemotherapy and then relapse; it is likely that not all of these patients require salvage chemotherapy followed by a transplant. For advanced-stage patients, an ongoing randomized study is comparing ABVD with brentuximab vedotin plus AVD; it is possible that patients who relapse after brentuximab vedotin plus AVD will be more difficult to cure.[3]

Table 5. Deauville Criteria

Score 1: No uptake
Score 2: Uptake ≤ mediastinum
Score 3: Update > mediastinum but ≤ liver
Score 4: Uptake > liver at any site
Score 5: Uptake > liver and new sites of disease
Score X: New areas of uptake unlikely to be related to lymphoma

Data from Meignan M et al. *Leuk Lymphoma*. 2009;50(8):1257-1260.[4]

The Role of PET Imaging

PET imaging is involved in many aspects of Hodgkin lymphoma management and has changed the definitions of response and remission. The 5-point Deauville criteria are used to identify remission and assess response to treatment

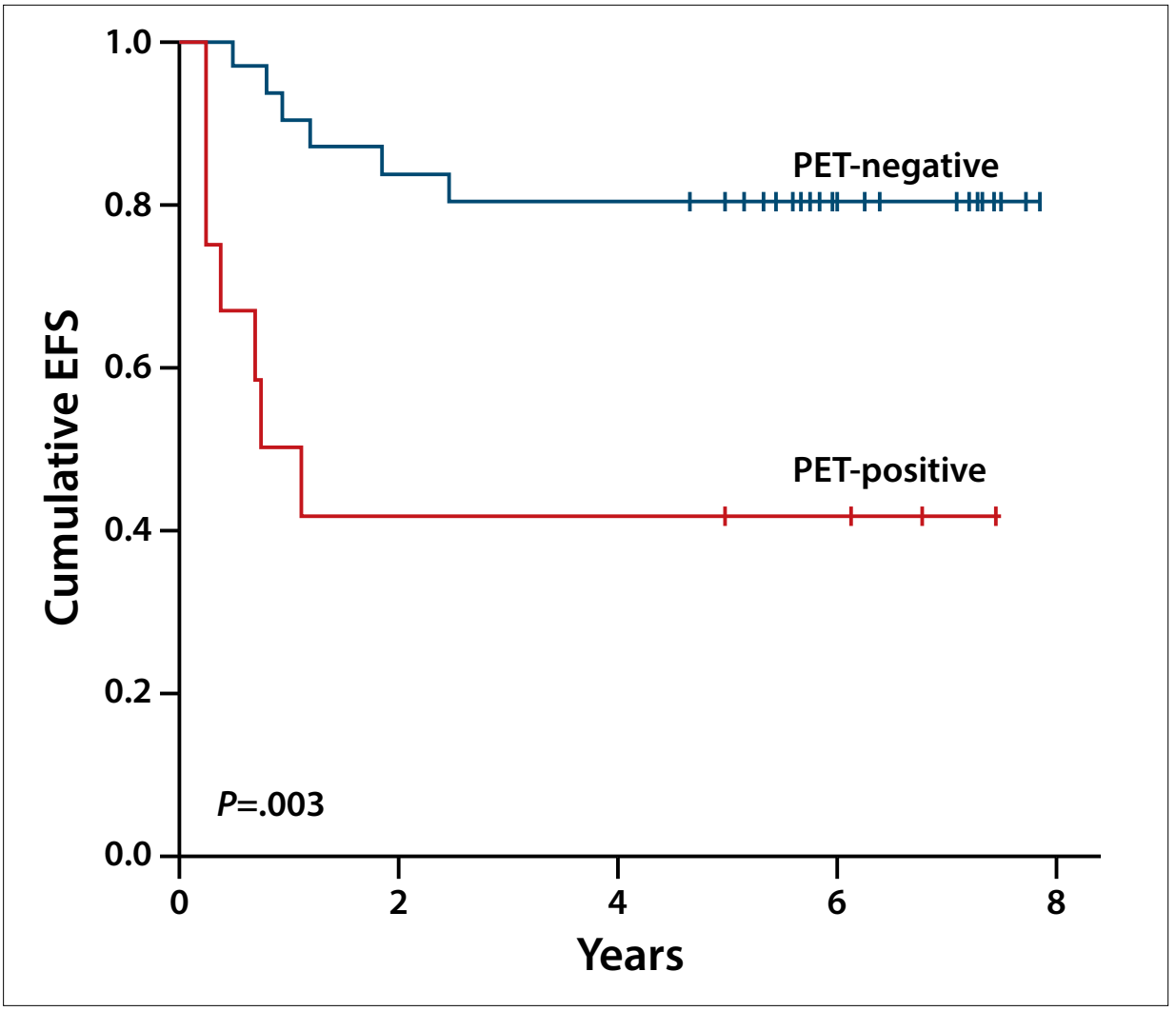

Figure 1. Event-free survival (EFS) according to positron emission tomography (PET) status before stem cell transplantation in patients with relapsed/refractory Hodgkin lymphoma. Republished with permission of *Blood* from Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma.[5] Moskowitz AJ et al, volume 116, issue 23. ©2010. Permission conveyed through Copyright Clearance Center, Inc.

(Table 5).[4] In 2010, Alison J. Moskowitz, MD, from our group at Memorial Sloan Kettering Cancer Center, published a landmark paper in *Blood* showing that patients who had a negative PET scan prior to stem cell transplantation had a 75% chance of being cured (Figure 1).[5] In contrast, patients with a positive PET scan, despite improvement on a CT scan, had a 31% chance of being cured.

For most investigators who treat patients with curative Hodgkin lymphoma in a relapsed setting, the goal of second-line therapy is to normalize the PET image. Several studies from the past 10 years have evaluated approaches to this goal. Standard chemotherapy, such as ICE chemotherapy or DHAP chemotherapy, has been studied by groups including Memorial Sloan Kettering Cancer Center and the German Hodgkin Study Group.[6,7] Although 2 cycles of this salvage therapy will achieve a complete response in approximately 50% to 60% of patients, the associated toxicity has driven the need for other treatments. Two approaches under investigation are sequential therapy and the use of a less toxic but equally effective combination.

Use of Brentuximab Vedotin in the Pretransplant Setting

Recent studies in the pretransplant setting have described 3 different strategies using brentuximab vedotin that will likely be practice-changing in the next few years. A study of sequential therapy was reported by Robert W. Chen, MD, from the City of Hope. In this clinical trial, patients with relapsed or refractory Hodgkin lymphoma received

standard brentuximab vedotin.[8] Patients who achieved a complete response went on to transplant. Patients who achieved a partial response received more treatment, for up to 4 cycles. This treatment consisted of another therapy, such as ICE or DHAP. After 2 cycles of brentuximab vedotin, 30% of the patients had a complete response and proceeded to transplant. The overall response rate to brentuximab vedotin was 70%. Unfortunately, among the patients with a partial response to brentuximab vedotin who received 2 more cycles of therapy, none converted to a complete response, and all still needed standard salvage treatment. In an amendment to the trial, the dosage of brentuximab vedotin will be increased in patients who do not achieve a complete response after the second cycle.

At the Memorial Sloan Kettering Cancer Center, we conducted a trial in which brentuximab vedotin was given weekly at 1.2 mg/kg for 3 weeks followed by 1 week of rest, and then again for 3 weeks with 1 week of rest followed by imaging.[9] Patients who had a negative PET scan went on to transplant. Patients with a positive PET scan were crossed over to ICE chemotherapy (in contrast to the trial by Chen and colleagues,[8] in which the type of chemotherapy varied). Approximately one-third of the patients had a complete response to brentuximab vedotin, and 80% of the patients had a complete response to either brentuximab vedotin alone or brentuximab vedotin followed by ICE. Among the patients in remission who proceeded to transplant, 80% were in remission 2 years after transplant.[10]

Another option is to combine brentuximab vedotin with a less-toxic treatment. At the 2014 ASH meeting, Ann LaCasce, MD, presented results of a phase 1B/2 study combining brentuximab vedotin with bendamustine.[11] In a previous trial, our group at Memorial Sloan Kettering had shown that in patients with relapsed/refractory Hodgkin lymphoma, bendamustine achieved a response rate of more than 50%, but the response duration was brief.[12] It was hoped that the combination of bendamustine and brentuximab vedotin would improve the complete remission rate and possibly allow more patients to proceed to transplant. As reported by Dr LaCasce, the complete response rate was very high, at more than 80%, and many of the patients underwent transplant. It appears that the combination was well tolerated, with the exception of a high rate of infusion-related reactions, which led to a protocol amendment requiring premedication with corticosteroids and antihistamines.

The AETHERA Trial

In 2009, the AETHERA study group—a consortium of 78 centers worldwide—designed the only placebo-controlled, random-assignment trial in Hodgkin lymphoma.[13] The trial aimed to determine whether patients at risk for relapse after ASCT would benefit from the addition of consolidation therapy with brentuximab vedotin.

Risk Factors

The issue of risk in Hodgkin lymphoma is complicated. In the past 20 years, the results of ASCT for Hodgkin lymphoma have maintained a plateau, with a cure in approximately 50% of patients.[14-17] Several risk factors are used to determine whether a patient should undergo transplant. Reports in the literature have attempted to predict outcome based on pre–salvage therapy risk factors and pretransplant risk factors. Overwhelmingly, the most important risk factor is whether a patient achieves remission (a state known as primary refractory Hodgkin lymphoma) after a full course of ABVD or BEACOPP. Another important risk factor is the presence of disease outside of the lymph node system. According to the German Hodgkin Study Group, all patients with stage 4 disease are at poor risk at the time of relapse. Other groups, including the Memorial Sloan Kettering Cancer Center, consider the presence of extranodal sites of involvement to indicate poor risk, meaning that patients with relapsed or refractory Hodgkin lymphoma before salvage chemotherapy who show disease in the lung, liver, or bone in a staging evaluation have a worse prognosis than patients with only nodal disease. A number of groups have suggested that patients who have active B symptoms, such as fever, night sweats, and weight loss, at the time of salvage chemotherapy also have an unfavorable prognosis. This theory has not been borne out at many centers because the assessment of B symptoms tends to be somewhat subjective.

The presence of primary refractory disease, extranodal disease at the time of relapse, and B symptoms supersedes the prognostic factor analyses performed at the time of salvage chemotherapy. The AETHERA trial also included remission duration of less than a year as a prognostic factor because at the time of the trial design, there were many patients with a late relapse who went on to transplant. More recent experience suggests that response duration may not be useful for prognosis because the dramatic improvement in primary therapy means that most patients now have a remission duration of less than a year when they undergo transplantation. When patients fail primary therapy, it is usually early in the course of management.

Pre–salvage therapy risk factors appear to be less important than pretransplant remission status. Prognosis is improved among patients who achieve remission after salvage chemotherapy as confirmed by a negative PET image.[5] The value of this prognostic factor is seen across almost all salvage regimens, including ICE, DHAP, single-agent brentuximab vedotin, and combinations incorporating brentuximab vedotin. The goal of salvage chemotherapy should be a complete response as shown by a negative PET scan.

Table 6. PFS* in the AETHERA Trial

	Brentuximab Vedotin (n=165)	Placebo (n=164)
Hazard ratio (95% CI)	0.50 (0.36-0.70)	
Events	60	89
Median PFS (months)	Not reached	16
2-Year PFS rate	65%	45%

*Per investigator review.

AETHERA, A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant; PFS, progression-free survival.

Data from Moskowitz CH et al. The AETHERA trial: results of a randomized, double-blind, placebo-controlled phase 3 study of brentuximab vedotin in the treatment of patients at risk of progression following autologous stem cell transplant for Hodgkin lymphoma [ASH abstract 673]. *Blood*. 2014;124(suppl 21).[13]

Design of the AETHERA Trial

The AETHERA trial included centers throughout the world. Because many countries did not have access to PET scans, pretransplant remission status could not be dictated.[13] The trial therefore relied on pre–salvage chemotherapy risk factors: remission duration of less than a year, primary refractory disease, and extranodal sites of involvement. Patients were eligible to receive posttransplant consolidation treatment if they had at least 1 of these risk factors and if their transplant had been performed in the setting of complete remission, partial remission, or stable disease. The AETHERA trial compared 16 doses of brentuximab vedotin vs placebo after a stem cell transplant in at-risk patients.

Results of the AETHERA Trial

The goal of the AETHERA study was to improve progression-free survival, which almost always translates to overall survival at 4 to 5 years after transplantation. Among patients who are in remission at 2 years after a stem cell transplantation, almost 95% will likely be cured. In AETHERA, 65% of the patients who received brentuximab vedotin posttransplant were progression-free at 2 years, compared with 45% who received placebo (Table 6).[13] The AETHERA investigators believe that the use of consolidation therapy with brentuximab vedotin posttransplant will be beneficial in patients with remission duration of less than a year, primary refractory disease, or extranodal sites of involvement.

In general, brentuximab vedotin was fairly well tolerated when given in a consolidative fashion. AETHERA is the first study in the aggressive lymphomas—including diffuse large B-cell lymphoma and peripheral T-cell lymphoma—in which a new drug that was added to the backbone of a transplant program in a placebo-controlled fashion showed improvement in progression-free survival. We believe that this approach has the potential to become the standard of care in this patient population.

Relapsed Disease After Transplant

In previous years, patients who developed disease after transplant could receive treatment with brentuximab vedotin. Moving forward, this strategy will likely evolve because brentuximab vedotin is now being administered before transplant and as posttransplant consolidation therapy. PD-1 inhibitors may be an option for these patients.

The ASH 2014 meeting featured presentations on 2 exciting PD-1 inhibitors: nivolumab and pembrolizumab.[18-20] These agents bind to PD-1, which is expressed on the surface of activated T cells. Its ligands are PD-L1 and PD-L2, which are expressed on many tumor cells. Nivolumab and pembrolizumab are immunoglobulin G4 monoclonal antibodies to PD-1. Nivolumab is human, and pembrolizumab is humanized. In classical Hodgkin lymphoma, a common genetic abnormality in the Reed-Sternberg cell is amplification of chromosome 9p24.1, which results in overexpression of PD-L1 and PD-L2. It would therefore make sense that the PD-1 inhibitors should be active in patients with this disease.

The ASH studies provided data on nivolumab and pembrolizumab in Hodgkin lymphoma cohorts taken from studies including different types of lymphoma.[18-20] In summary, between 80% and 90% of patients achieved clinical benefit from these treatments. The complete response rate ranged from 20% to 30%, and the partial response rate ranged from 30% to 45%. There were also patients who achieved prolonged stable disease. Many of the patients still have ongoing responses, and the median duration of response has not been reached.

Longer follow-up with these agents is necessary. The optimum length of therapy must be determined. It is not known whether patients should be taken off treatment and considered for allogeneic stem cell transplantation. In the relapsed and refractory setting, however, many centers want to combine brentuximab vedotin with a checkpoint inhibitor—both pretransplant and posttransplant—to determine whether response rates and/or progression-free survival can be improved. The combination of brentuximab vedotin and nivolumab will be evaluated in 2 phase 1/2 clinical trials, one in patients with relapsed or refractory Hodgkin lymphoma and the other in patients with relapsed or refractory B-cell and T-cell non-Hodgkin lymphomas, including diffuse large B-cell lymphoma.

Disclosure

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References

1. SEER State Fact Sheets: Hodgkin Lymphoma. Surveillance, Epidemiology, and End Results Program. http://seer.cancer.gov/statfacts/html/hodg.html. Accessed December 22, 2014.
2. Radford J, O'Doherty M, Barrington S, et al. UK NCRI RAPID trial in patients with clinical stage IA/IIA Hodgkin lymphoma: an update following attainment of the recruitment target [abstract 107]. Paper presented at: 3rd International Workshop on Interim-PET in Lymphoma. September 26-27, 2011; Menton, France.
3. ClinicalTrials.gov. Phase 3 frontline therapy trial in patients with advanced classical Hodgkin lymphoma. https://clinicaltrials.gov/ct2/show/NCT01712490. Identifier: NCT01712490. Accessed December 22, 2014.
4. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. *Leuk Lymphoma*. 2009;50(8):1257-1260.
5. Moskowitz AJ, Yahalom J, Kewalramani T, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Blood*. 2010;116(23):4934-4937.
6. Zelenetz AD, Hamlin P, Kewalramani T, Yahalom J, Nimer S, Moskowitz CH. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. *Ann Oncol*. 2003;14(suppl 1):i5-i10.
7. Josting A, Rudolph C, Mapara M, et al. Cologne high-dose sequential chemotherapy in relapsed and refractory Hodgkin lymphoma: results of a large multicenter study of the German Hodgkin Lymphoma Study Group (GHSG). *Ann Oncol*. 2005;16(1):116-123.
8. Chen RW, Palmer J, Martin P, et al. Results of a phase II trial of brentuximab vedotin as first line salvage therapy in relapsed/refractory HL prior to AHCT [ASH abstract 501]. *Blood*. 2014;124(suppl 21).
9. Moskowitz A, Heiko H, Gerecitano JF, et al. FDG-PET adapted sequential therapy with brentuximab vedotin and augmented ICE followed by autologous stem cell transplant for relapsed and refractory Hodgkin lymphoma [ASH abstract 2099]. *Blood*. 2013;122(21 suppl).
10. Moskowitz AJ, Schöder H, Yahalom J, et al. *Lancet Oncol*. In press.
11. LaCasce A, Bociek RG, Matous J, et al. Brentuximab vedotin in combination with bendamustine for patients with Hodgkin lymphoma who are relapsed or refractory after frontline therapy [ASH abstract 293]. *Blood*. 2014;124(suppl 21).
12. Moskowitz AJ, Hamlin PA Jr, Perales MA, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2013;31(4):456-460.
13. Moskowitz CH, Nadamanee A, Masszi T, et al. The AETHERA trial: results of a randomized, double-blind, placebo-controlled phase 3 study of brentuximab vedotin in the treatment of patients at risk of progression following autologous stem cell transplant for Hodgkin lymphoma [ASH abstract 673]. *Blood*. 2014;124(suppl 21).
14. Sureda A, Constans M, Iriondo A, et al. Prognostic factors affecting long-term outcome after stem cell transplantation in Hodgkin's lymphoma autografted after a first relapse. *Ann Oncol*. 2005;16(4):625-633.
15. Majhail NS, Weisdorf DJ, Defor TE, et al. Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. *Biol Blood Marrow Transplant*. 2006;12(10):1065-1072.
16. Sirohi B, Cunningham D, Powles R, et al. Long-term outcome of autologous stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma. *Ann Oncol*. 2008;19(7):1312-1319.
17. Hahn T, McCarthy PL, Carreras J, et al. Simplified validated prognostic model for progression-free survival after autologous transplantation for hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2013;19(12):1740-1744.
18. Armand P, Ansell SM, Lesokhin AM, et al. Nivolumab in patients with relapsed or refractory Hodgkin lymphoma—preliminary safety, efficacy and biomarker results of a phase I study [ASH abstract 280]. *Blood*. 2014;124(suppl 21).
19. Lesokhin AM, Ansell SM, Armand P, et al. Preliminary results of a phase I study of nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies [ASH abstract 291]. *Blood*. 2014;124(suppl 21).
20. Moskowitz CH, Ribrag V, Michot J-M, et al. PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results from a phase 1b study (KEYNOTE-013) [ASH abstract 290]. *Blood*. 2014;124(suppl 21).

The Impact of the AETHERA Trial on Clinical Practice

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As previously discussed by Dr Moskowitz, the AETHERA trial was designed to determine whether Hodgkin lymphoma patients at risk for relapse would benefit from the addition of consolidation therapy with brentuximab vedotin after transplantation. The study found that 65% of patients who received brentuximab vedotin posttransplant were progression-free at 2 years, compared with 45% who received placebo.[1] These important results will influence the management of patients with Hodgkin lymphoma who receive high-dose therapy and undergo ASCT. The outcomes of patients with limited-stage Hodgkin lymphoma treated with primary chemotherapy or combined modality therapy are now very good; approximately 90% of these patients are cured.[2] A proportion of patients, however, either do not respond to first-line treatment or relapse and require further therapy. In these patients, high-dose therapy and stem cell transplantation has become the standard of care, with a cure rate of approximately 50% to 60%.[3,4] The AETHERA trial addressed a concept that has emerged over recent years: the possibility of identifying patients at higher risk of relapse after a stem cell transplantation to provide them with posttransplant therapy that could impact subsequent outcome.

The AETHERA trial incorporated a standard approach to identify patients at high risk of relapse.[1] Stud-

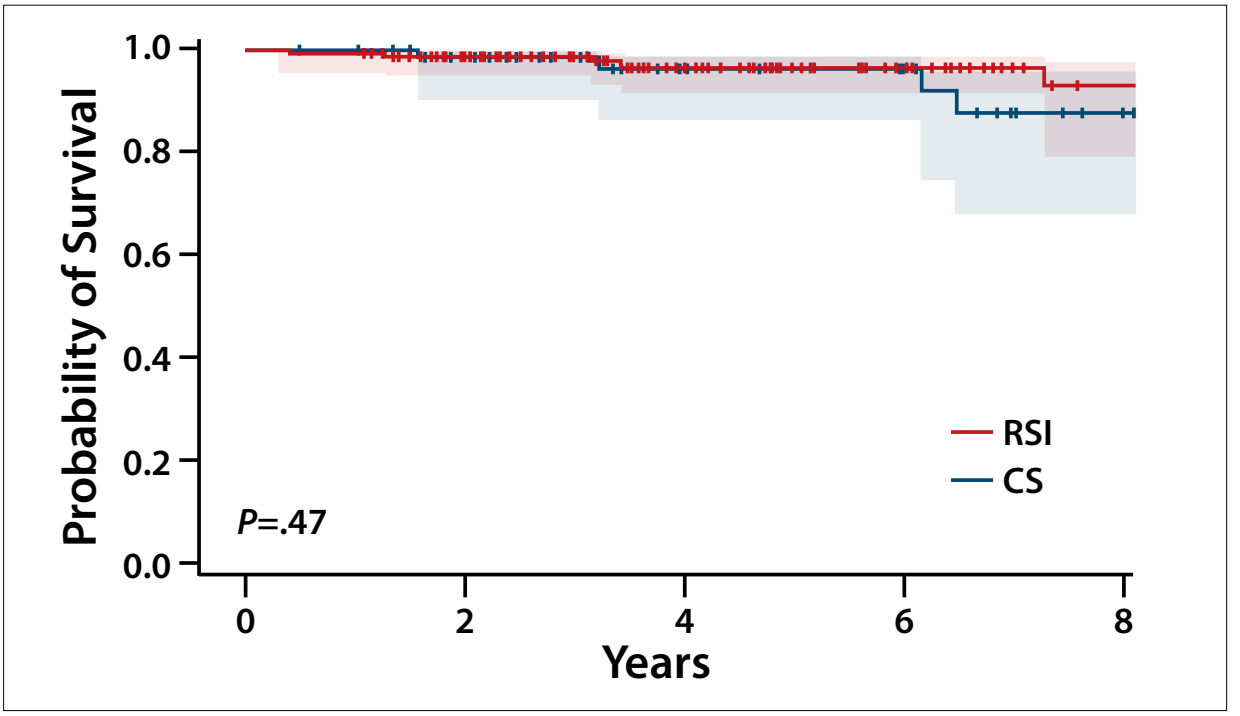

Figure 2. Overall survival in a study comparing routine surveillance imaging (RSI) and clinical surveillance (CS) in patients with classical Hodgkin lymphoma. Adapted from Pingali SR et al. Clinical or survival benefit to routine surveillance imaging for classical Hodgkin lymphoma patients in first complete remission [ASCO abstract 8505]. *J Clin Oncol*. 2013;31(15 suppl).[7]

ies have identified multiple risk factors for relapse, but the most consistent ones are primary refractory disease (meaning that the patient does not respond to first-line therapy) and relapse within 12 months of remission. Extranodal disease at the time of relapse also seems to be a risk factor. Emerging data suggest that patients with relapsed or refractory disease who have a positive PET scan following initial cytoreductive therapy are less likely to be cured by stem cell transplantation than those with PET-negative disease,[5] but this risk factor has not yet been confirmed prospectively. It will likely be the subject of a subset analysis of the trial.

The AETHERA study strongly suggests that patients with high-risk disease, however defined, will achieve a progression-free survival benefit with the use of a consolidation strategy that involves brentuximab vedotin after transplant.[1] This improvement has not yet translated into a difference in overall survival, and, based on observations in other transplant trials, any overall survival advantage may not emerge for many months.

Impact on Clinical Practice

The results of the AETHERA trial will likely lead many oncologists to use a consolidative strategy involving brentuximab vedotin. Although the definition of high risk will probably follow that used in the AETHERA study, these criteria are likely to vary and evolve. Patients with PET-positive disease who undergo transplantation are now more likely to be treated with brentuximab vedotin post-transplant, based on the assumption that the data from AETHERA can be extrapolated to other high-risk groups.

The trial raises the question of whether consolidation therapy with brentuximab vedotin might be beneficial among patients with low-risk disease. It seems likely that some oncologists will take the view that if this approach improves the outcome for high-risk patients, it will probably do the same for low-risk patients. Currently, there are no data to support this approach in low-risk patients, and the extent of any benefit is unknown.

The current approach to patients who undergo high-dose therapy is imperfect. Once patients have completed that therapy, the standard of care is a watch-and-wait approach without consolidation therapy. The exact form of the watch-and-wait approach varies. It generally involves clinical surveillance with repeat history, physical examination, and laboratory data. Intermittent imaging, which can include functional imaging or routine CT, is another common component. The effectiveness of this strategy is becoming less clear. Although specific data are lacking for posttransplant Hodgkin lymphoma patients, emerging data for the general Hodgkin population—as well as patients with other types of lymphoma—suggest that routine imaging surveillance is an insensitive way to identify relapse (Figure 2).[6,7] It is question-

able, therefore, whether a routine watch-and-wait approach that includes repetitive surveillance imaging is likely to be acceptable moving forward based on both its lack of effectiveness and concerns about long-term radiation exposure in this group of young patients.

The posttreatment surveillance strategy is evolving. Recurrence of Hodgkin lymphoma after transplant is usually identified by the patient's self-reported symptoms. There are questions regarding whether the addition of a consolidative strategy would affect this routine approach to surveillance. There are currently no data to indicate the best surveillance strategy for patients who are receiving posttreatment consolidation therapy.

For low-risk patients, the other unknown is the risk-benefit calculation. For patients with low-risk, recurrent Hodgkin lymphoma who undergo high-dose therapy and ASCT, the improvement in progression-free survival or overall survival must be balanced by the potential toxicities associated with a year of therapy with an agent such as brentuximab vedotin. Another unknown factor is whether insurance will cover consolidation therapy for patients with low-risk disease. A potential consequence of the AETHERA trial might be a reexamination of what constitutes high-risk disease in the hope that more patients will be able to obtain access to treatment with brentuximab vedotin. As subset analyses emerge from the AETHERA trial, it will be interesting to see whether the data identify groups of patients who benefit more from the use of brentuximab vedotin.

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Dr Sweetenham has received speaker's fees from Seattle Genetics and is a member of the Seattle Genetics advisory board.

References

1. Moskowitz CH, Nadamanee A, Masszi T, et al. The AETHERA trial: results of a randomized, double-blind, placebo-controlled phase 3 study of brentuximab vedotin in the treatment of patients at risk of progression following autologous stem cell transplant for Hodgkin lymphoma [ASH abstract 673]. *Blood*. 2014;124(suppl 21).
2. Armitage JO. Early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363(7):653-662.
3. Kuruvilla J. Standard therapy of advanced Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program*. 2009:497-506.
4. Kuruvilla J, Keating A, Crump M. How I treat relapsed and refractory Hodgkin lymphoma. *Blood*. 2011;117(16):4208-4217.
5. Moskowitz AJ, Yahalom J, Kewalramani T, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Blood*. 2010;116(23):4934-4937.
6. Pingali SR, Jewell SW, Havlat L, et al. Limited utility of routine surveillance imaging for classical Hodgkin lymphoma patients in first complete remission. *Cancer*. 2014;120(14):2122-2129.
7. Pingali SR, Jewell S, Havlat L, et al. Clinical or survival benefit to routine surveillance imaging for classical Hodgkin lymphoma patients in first complete remission [ASCO abstract 8505]. *J Clin Oncol*. 2013;31(15 suppl).

Recent Considerations in the Management of Hodgkin Lymphoma: Q&A

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H&O How is the management of Hodgkin lymphoma evolving?

JS Management of Hodgkin lymphoma is evolving in 3 major ways. There is now much more emphasis on a risk-directed approach to treatment. Many of the classic risk factors for Hodgkin lymphoma, such as anatomic stage, sedimentation rate, and the presence of B symptoms, are beginning to lose some of their prognostic significance in favor of some newer risk factors, such as functional imaging and biologic risk factors, including serum markers. Some of these newer risk factors are identified in tissue biopsies. Mainstream clinical management now includes PET functional imaging, but not yet biologic or serum markers.

Another change is that there is now a trend away from the use of radiation therapy whenever possible. Although some radiation oncologists might disagree, there appears to be mounting evidence suggesting that increasing numbers of patients probably do not need to receive radiation therapy, and can therefore avoid the late toxicities associated with that treatment. Use of the newer imaging modalities,

particularly functional imaging, may be a way to determine which patients require radiation therapy.

A third major change is the future possibility that some patients could be managed without conventional chemotherapy approaches. The activity of antibody-directed treatment, such as brentuximab vedotin, in Hodgkin lymphoma has been fairly impressive. We are also starting to see new results with agents that target some of the biologic pathways known to be important in Hodgkin lymphoma. For example, agents that target the PD-1 pathway are showing some early, promising activity in Hodgkin lymphoma.

H&O How can novel agents be evaluated?

JS The conventional approach to introducing new agents has been to initially assess them in patients who have relapsed or refractory disease and who have exhausted their curative options. Hodgkin lymphoma is very treatable and often curable. Use of novel agents in the frontline setting has inherent risk because the newer agents may be less effective than the standard of care. Clinical trials in the frontline setting will likely evaluate new agents in combination with standard treatment regimens. Because the outcome in Hodgkin lymphoma is so positive, clinical trials may require large numbers of patients to demonstrate benefit.

Another approach is to substitute a novel agent for one of the drugs in a conventional chemotherapy regimen. Brentuximab vedotin is being evaluated in this way. The randomized, phase 3 ECHELON-1 study of frontline treatment is comparing 2 versions of the standard of care, ABVD: one that follows the traditional regimen and one in which brentuximab vedotin replaces bleomycin.[1,2] This type of trial should be able to detect any differences in outcome. Although there is a concern that the omission of a drug from the standard of care could potentially put the patient at risk, close monitoring and appropriate safety rules will likely ameliorate this risk.

Another approach, which is also being used with brentuximab vedotin, is to treat patients with a novel agent for the initial 1 or 2 cycles of therapy, closely monitor them for response, and then follow up with standard treatment.[3] A potential advantage to this approach is that it provides an early signal as to whether the new drug has activity in the frontline setting while minimizing any risk because the standard regimen will be administered soon after. This approach will then have to be converted into a randomized clinical trial. There are some early data, available in abstract form, showing that single-agent brentuximab vedotin has clinical activity in the frontline setting in patients who then go on to receive standard chemotherapy.

H&O Are there any challenges in knowing when patients are cured?

JS There is currently no single test that reliably signals cure for our patients. Several tests are administered at the end of treatment that have predictive value. Functional imaging is the best test now available. A negative PET scan indicates with 80% to 90% certainty that a patient will not relapse. A positive PET scan is associated with a 40% to 60% chance of relapse. Ultimately, the only real determinant of cure is when the patient does not relapse. In general, 5-year survival is regarded as a reasonably good metric that correlates with cure. It is rare for patients to relapse after 5 years.

H&O What are some promising areas of future research?

JS There is some preliminary evidence that drugs targeting the PD-1 pathway are active in Hodgkin lymphoma. Early data from gene-profiling studies suggest that the tumor microenvironment is important to prognosis and perhaps to the underlying mechanism of Hodgkin lymphoma. There has been a concept that Hodgkin Reed-Sternberg cells survive because of signals that they pick up from the surrounding inflammatory infiltrate. As we understand more of the signals within the microenvironment, we will likely see more treatment modalities, such as PD-1 inhibitors, that are aimed at the interaction between the microenvironment and the malignant cells.

Disclosure

Dr Sweetenham has received speaker's fees from Seattle Genetics and is a member of the Seattle Genetics advisory board.

References

1. Ansell SM, Younes A, Connor JM, et al. Phase 3 study of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as front-line treatment for advanced classical Hodgkin lymphoma (HL): ECHELON-1 study [ASCO abstract TPS8613]. *J Clin Oncol.* 2014;32:5(suppl).

2. ClinicalTrials.gov. Phase 3 frontline therapy trial in patients with advanced classical Hodgkin lymphoma. https://clinicaltrials.gov/ct2/show/NCT01712490. Identifier: NCT01712490. Accessed December 24, 2014.

3. Federico M, Pesce EA, Merli F, et al. A pilot phase II study with brentuximab vedotin followed by ABVD in patients with previously untreated Hodgkin lymphoma: a preliminary report [ASCO abstract 8507]. *J Clin Oncol.* 2014;32:5(suppl).

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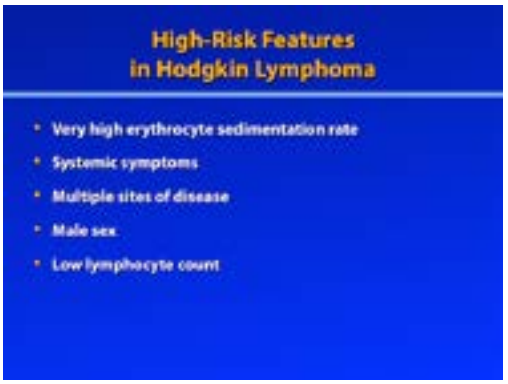

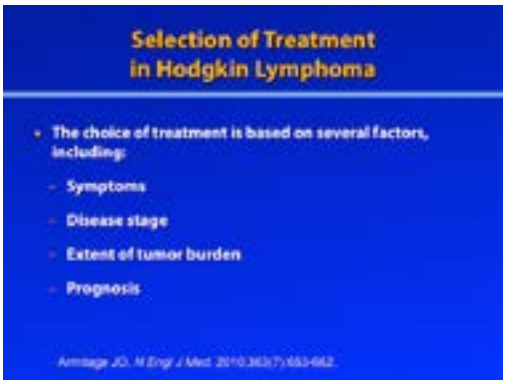

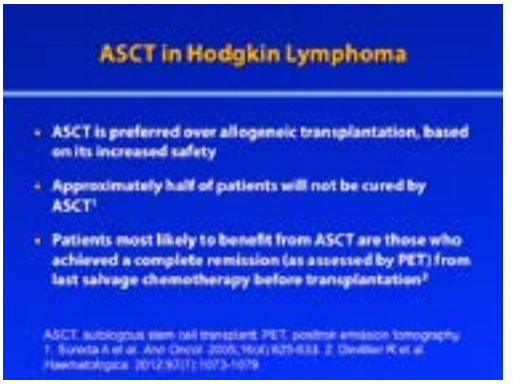

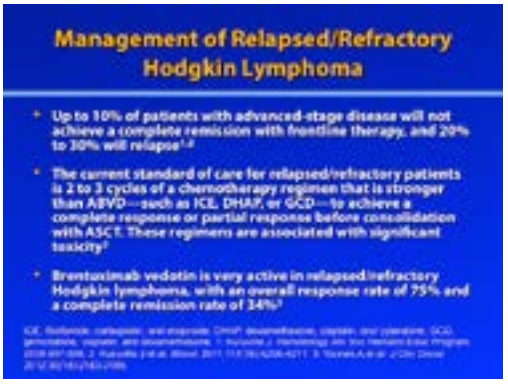

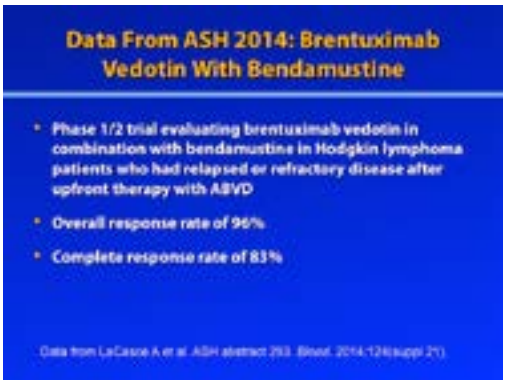

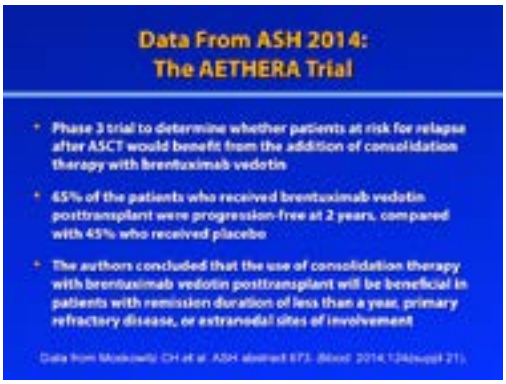

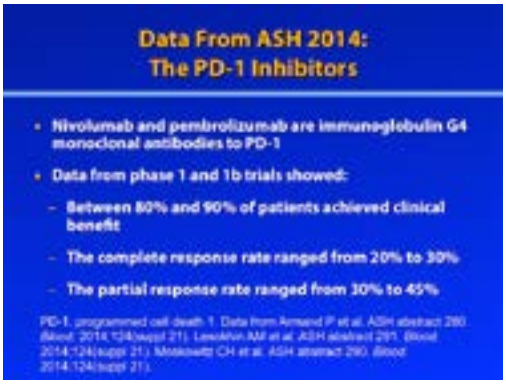

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