Hodgkin Lymphoma: A Review and Update on Recent Progress

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Abstract: Hodgkin lymphoma (HL) is a unique hematopoietic neoplasm characterized by cancerous Reed-Sternberg cells in an inflammatory background. Patients are commonly diagnosed with HL in their 20s and 30s, and they present with supra-diaphragmatic lymphadenopathy, often with systemic B symptoms. Even in advanced-stage disease, HL is highly curable with combination chemotherapy, radiation, or combined-modality treatment. Although the same doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapeutic regimen has been the mainstay of therapy over the last 30 years, risk-adapted approaches have helped de-escalate therapy in low-risk patients while intensifying treatment for higher risk patients. Even patients who are not cured with initial therapy can often be salvaged with alternate chemotherapy combinations, the novel antibody-drug conjugate brentuximab, or high-dose autologous or allogeneic hematopoietic stem cell transplantation. The programmed death-1 inhibitors nivolumab and pembrolizumab have both demonstrated high response rates and durable remissions in patients with relapsed/refractory HL. Alternate donor sources and reduced-intensity conditioning have made allogeneic hematopoietic stem cell transplantation a viable option for more patients. Future research will look to integrate novel strategies into earlier lines of therapy to improve the HL cure rate and minimize long-term treatment toxicities. CA Cancer J Clin 2018;68:116-132. © 2017 American Cancer Society.

Keywords: allogeneic stem cell transplantation, antibody-drug conjugate, brentuximab, Hodgkin lymphoma, immunotherapy, positron emission tomography (PET)-adapted therapy, programmed death 1 (PD-1) inhibitor

Introduction

The first descriptions of what came to be known as Hodgkin disease date back to 1832, when the eminent British pathologist Thomas Hodgkin described an autopsy case series of patients with lymphadenopathy and splenic enlargement.1 It was not until the late 1990s that our understanding of the entity as a malignancy arising from germinal center or postgerminal center B cells led to the term Hodgkin lymphoma (HL) gaining favor.2 Characteristically, the cancer cells form a minority of the tumor and are surrounded by a reactive inflammatory milieu comprising lymphocytes, eosinophils, neutrophils, histiocytes, and plasma cells. These malignant cells can be pathognomonic, multinucleate giant cells or large mononuclear cells and, together, are referred to as Hodgkin and Reed-Sternberg (HRS) cells.

It is estimated that HL accounts for approximately 10% of cases of newly diagnosed lymphoma in the United States (8260 of 80,500 cases), and the remainder are non-Hodgkin lymphoma (NHL). Of 21,210 estimated deaths yearly because of lymphoma, about 1070 (or 5%) are from HL. It accounts for about 0.5% of newly diagnosed cases of cancer in the United States and about 0.2% of all cancer deaths. However, lymphoma is the most common cancer diagnosed in adolescents (aged 15–19 years), accounting for 21% of new diagnoses, almost two-thirds of which are HL.3
Epidemiology and Pathogenesis
Males are expected to comprise about 56% of patients newly diagnosed with HL in 2017. The median age of diagnosis is 39 years; HL is most frequently seen in the group ages 20 to 34 years, which makes up almost one-third of new diagnoses. The incidence rates do not seem to vary between white and black Americans (3.1 new cases per 100,000 males) but are about one-half as much in Asians/Pacific Islanders (1.6 new cases per 100,000 males) and American Indians/Alaskan Natives. Incidence rates are also lower in Hispanic Americans (2.6 new cases per 100,000 males) compared with white and black populations. Incidence rates of HL have stayed flat since the mid-1970s, but mortality rates have steadily declined from 1.3 cases per 100,000 in 1975 to 0.3 cases per 100,000 in 2014. Across all stages of diagnosis, the relative 5-year survival of patients with HL has improved from 70% to 85% during the same period.

The etiology of HL is not well understood. Epstein-Barr virus (EBV) is a ubiquitous gammaherpesvirus spread mainly through saliva and is the causative agent for infectious mononucleosis. EBV-encoded small RNAs are noncoding RNAs expressed abundantly in latently EBV-infected cells and can be detected by in situ hybridization. EBV is detected in HRS cells in a majority of HL specimens from the developing world but much less frequently in the industrialized countries of North America and Western Europe. The risk of developing EBV-positive HL is significantly increased (relative risk, 4.0; 95% confidence interval [95% CI], 3.4-4.5) after an episode of infectious mononucleosis, with an estimated median incubation time of 4.1 year (95% CI, 1.8-8.3 years). However, the absolute risk of developing EBV-positive HL is significantly increased (relative risk, 4.0; 95% confidence interval [95% CI], 1.8-8.3 years) after an episode of infectious mononucleosis. EBV-encoded small RNAs are noncoding RNAs expressed abundantly in latently EBV-infected cells and can be detected by in situ hybridization. EBV is detected in HRS cells in a majority of HL specimens from the developing world but much less frequently in the industrialized countries of North America and Western Europe.

Immunosuppression in a variety of medical conditions increases the risk of HL. The incidence of HL is significantly higher in the human immunodeficiency virus (HIV)-infected population than in the general population (standardized rate ratio, 14.7 in a US study). The advent of highly active antiretroviral therapy (HAART) has indirectly led to the increase in rates of HL in HIV-infected patients, with the standardized rate ratio increasing from 11.7 (1992-1995) to 17.9 (2000-2003). Most cases are EBV-positive and can occur in patients who have normal CD4 counts with a more aggressive histological phenotype; however, survival in HIV-associated HL has improved significantly in the post-HAART period.

The incidence of HL also increases after solid organ transplantation and in patients with a history of autoimmune conditions, such as rheumatoid arthritis (odds ratio [OR], 2.7), systemic lupus erythematosus (OR, 5.8), and sarcoidosis (OR, 14.1).

Classification
HL is subdivided into classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL) based on morphology and immunohistochemistry. Over 90% of cases are of cHL, which behaves as an aggressive neoplasm, whereas lymphocyte-predominant HL (LPHL) has an indolent biology in most instances. The major focus of this review is cHL, which itself is subdivided into 4 histologic subtypes based on morphology, the abundance of HRS cells, and the background infiltrate. The malignant HRS cell in all subtypes of cHL exhibits a characteristic immunophenotypic pattern of CD15-positive, CD30-positive, and CD45-negative.

Nodular Sclerosis
Nodular sclerosis cHL (NSCHL) is the most common subtype, accounting for about 70% of cHL cases in the developed world and characterized by neoplastic lacunar-type HRS cells in an inflammatory background of band-forming sclerosis. Mediastinal adenopathy is seen in 80% of cases, and bulky nodes (>10 cm in diameter) are present in about one-half of patients. Association with Epstein-Barr virus is less frequent, and NSCHL has a better prognosis overall than other types of cHL.

Mixed Cellularity
Mixed-cellularity cHL (MCCHL) comprises 20% to 25% of cHL in the United States but is more frequent in patients with HIV infection and in developing countries. The HRS cells are scattered in a diffuse, mixed, inflammatory background without sclerosing fibrosis. Epstein-Barr–encoded latent membrane protein 1 and EBV small nuclear RNA transcripts are expressed much more frequently (approximately 75% of cases) than in NSCHL.

Lymphocyte Rich
Lymphocyte-rich cHL comprises about 5% of all cHL; specimens have scattered HRS cells within a nodular or diffuse cellular background of small lymphocytes and without neutrophils or eosinophils. Patients tend to have peripheral adenopathy without bulky mediastinal involvement and usually present with early-stage disease. Treatment outcomes are excellent using modern combination chemotherapy regimens, with rare treatment failures.

Lymphocyte Depleted
Lymphocyte-depleted cHL is the rarest cHL subtype in the developed world, accounting for <1% of cases. Tumor specimens are diffusely infiltrated by HRS cells and are without a significant reactive inflammatory infiltrate. It is often seen in association with HIV infection and has a more aggressive disease course compared with the other cHL subtypes.
Overall, patients who have lymphocyte-depleted cHL and mixed-cellularity cHL have a significantly worse prognosis compared with patients who have NSCHL, whereas patients who have lymphocyte-rich cHL have the best prognosis. In addition to subtyping, grading systems that incorporate tumor characteristics, such as extent of infiltration by the malignant HRS cells, eosinophilia, and lymphocyte depletion, have been developed and are prognostic of outcomes but are not frequently used.

Clinical Presentation and Initial Workup
HL is most commonly diagnosed in the group ages 20 to 34 years, accounting for 31% of new cases; however, it can be seen across the age spectrum, from adolescents to the elderly. Painless lymphadenopathy enlarging over months is a common mode of presentation. The 3 most common sites of disease presentation—mediastinal involvement, or left neck nodal enlargement, or right neck nodal enlargement—are each seen in about 60% of patients (not mutually exclusive). Other sites include splenic, axillary, abdominal, hilar, or inguinal/femoral, in descending order of frequency. Mediastinal masses can grow quite large before a diagnosis is made; bulky disease is defined by transverse diameter of the tumor mass exceeding 10 cm and confers a poorer prognosis in patients with early-stage disease. B symptoms—fevers, chills, night sweats, or unexplained weight loss >10% of body weight—are frequent in patients with advanced-stage or bulky disease and are prognostic; therefore, they are included in the staging system. Severe, unremitting pruritus without obvious skin pathology on examination can be resistant to topical and systemic agents and can be an early clue to the presence of clinically occult HL.

Inflammatory markers, such as the erythrocyte sedimentation rate, can be elevated at diagnosis and can serve as a useful laboratory marker of disease response. Similarly, leukocytosis/neutrophilia and anemia can be seen in patients with extensive disease and portend a poorer prognosis. Excisional biopsy of the involved lymph node (or, less commonly, an involved extranodal site or bone) is preferred to establish a definitive diagnosis. Occasionally, core needle biopsies are adequate, but the smaller biopsy specimens are often inadequate for definitive diagnosis insofar as HRS cells may be missed in these specimens, and assessment of architecture may be suboptimal. Whereas core needle biopsies in some circumstances establish a diagnosis, fine-needle aspirates never reveal architecture and, because the malignant cells of HL are not detected by flow cytometry, fine-needle aspirate is never sufficient for a new diagnosis.

Staging Hodgkin Lymphoma
The Ann Arbor staging system with Cotswolds modification has been in use since 1989 but has incorporated somewhat antiquated procedures, such as liver biopsy, laparotomy, and bone marrow trephine, for initial staging. Fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) has very high sensitivity and specificity in HL—an international workshop in Deauville, France, helped establish a consensus on simple, reproducible criteria for PET interpretation in HL. The resultant 5-point Deauville scale helped pave the way for risk-adapted therapy based on interim PET findings and later helped establish the role of PET-CT at initial staging and at the end of treatment. The Lugano classification in 2014 modernized staging for lymphomas, and FDG PET-CT was formally incorporated into standard staging. A modification of the Ann Arbor descriptive terminology is used for anatomic distribution of disease extent, but treatment is based on classifying patients as having limited (stages I and II, nonbulky) or advanced (stage III or IV) disease, with stage II bulky disease considered as limited or advanced disease based on histology and other prognostic factors (Table 1).

The Lugano staging and response assessment is fairly new and not yet universally accepted, as most major studies have used the Deauville scale. FDG PET-CT has also supplemented the utility of bone marrow biopsy in HL; in a large, retrospective study, no patients with bone marrow involvement were assessed as having limited stage disease on PET-CT. Although there were a few cases in which patients were upstaged from stage III on PET-CT to stage IV based on bone marrow involvement, management did not change in any patients, because advanced-stage HL is treated similarly regardless of stage.

Treatment of Newly Diagnosed HL
Chemotherapy and radiation are the mainstays of cHL treatment, unlike some types of indolent NHL, in which observation is an option. Before the advent of combination chemotherapy, this was a relentless and invariably fatal malignancy with a 5-year survival of less than 10%. Advances in understanding the biology of the disease and improvement in modalities of chemotherapy and radiotherapy have improved survival across the board in every stage of cHL (Fig. 1 and 2). It is a highly curable malignancy—the 5-year relative survival for patients diagnosed with cHL at ages birth to 19 years is 96.4%, and it is 89.8% for those diagnosed between ages 20 and 64 years (2007-2013 Surveillance, Epidemiology, and End Results data).

Radiotherapy had been used to treat HL (then termed Hodgkin disease) since the early 1900s, but it took several decades for a better understanding of the patterns of spread and the fields and doses of radiation that would be required to turn a palliative measure into a potentially curative treatment. Development of the high-energy linear accelerator at Stanford in the 1950s allowed for more precise fields and accurate dose delivery. Because, in most cases, cHL spreads
to contiguous nodal sites, fields involved by tumor and adjacent fields could be irradiated, allowing cure of many patients with early-stage and, in some cases, advanced-stage disease.31,32 Involved-field radiation (treating only sites of gross disease) was replaced by extended-field radiation, in which regions adjacent to known sites of disease were also treated. Mantle-field radiation (covering neck, axillae, mediastinum, and hilar regions), along with the inverted-Y field to treat the abdomen and spleen, together formed total nodal irradiation. A Stanford study demonstrated 80% long-term freedom from progression for patients who received total nodal irradiation, but it came with a high risk of long-term radiation-related toxicities.33,34 Involved-site and involved-node radiation fields were developed in the 3-dimensional and PET-directed radiotherapy era to minimize toxicities of radiotherapy.

Early trials with single-agent cytotoxic chemotherapeutics like mechlorethamine, chlorambucil, and cyclophosphamide produced promising response rates of 50%, but none of these

| STAGE | INVOLVED SITES |
|-------|---------------|
| Limited stage favorable | One lymph node or a group of adjacent lymph nodes |
| IIA | Two or more nodal groups on the same side of the diaphragm |
| Limited stage unfavorable | Limited stage with additional risk factors* |
| IIA | > 3-4 lymph node areas |
| IIB | Elevated ESR |
| IIA | Advanced age |
| IIIB | ≥ 1 extranodal site(s) |
| IIB | B symptoms |
| Advanced stage | Single nodal mass, in contrast to multiple smaller lymph nodes, of 10 cm or greater than one-third of the transthoracic diameter at any level of thoracic vertebrae |
| II | Lymph nodes on both sides of the diaphragm; lymph nodes above the diaphragm with spleen involvement |
| III | Additional, noncontiguous extralymphatic involvement (eg, for lung, liver, or skeletal metastases) |

Abbreviation: ESR, erythrocyte sedimentation rate.

*Risk factors are defined differently by various study groups.
responses were durable despite prolonged courses of maintenance chemotherapy. The discovery of novel drugs like the vinca alkaloids and procarbazine led to the advent of combination chemotherapy. Nitrogen mustard (mechlorethamine), vincristine, procarbazine, and prednisone (MOPP) was developed at the National Cancer Institute (NCI) by Vincent DeVita’s group; 6 months of MOPP resulted in 81% of patients with newly diagnosed advanced cHL achieving complete remission. Treatment paradigms shifted from continuous therapy to a defined endpoint, as about one-half the complete responders were disease free 4 years after completion.

MOPP was superior to extended-field radiation therapy for the treatment of patients with stages IB, IIA, IIB, or IIIA cHL—although complete remission rates were similar in both arms (96%), relapses were fewer with MOPP (13% vs 35%). The projected 10-year disease-free survival of patients who were randomized to receive radiation was 60% versus 86% (P = .009) for those who received MOPP.

Simultaneously to the development of MOPP at the NCI, the Italian Istituto Nazionale Tumori under Gianni Bonnadonna developed a combination regimen with the newly discovered chemotherapeutic drugs doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) based on their individual antilymphoma activity and nonoverlapping toxicities. When compared, the 2 regimens produced comparable results—6 cycles of either MOPP or ABVD yielded similar complete remission rates of about 75% in patients with advanced cHL. Despite their noncross-resistant chemosensitivity profiles, alternating monthly cycles of MOPP and ABVD over 12 months did not improve upon the long-term cure rates of either regimen when given alone over 6 to 8 months. In a large, multicenter trial of patients with advanced cHL, the complete response (CR) rate was 67% in the MOPP group, 82% in the ABVD group, and 83% in the MOPP-ABVD group (P = .006 for the comparison between MOPP and the other 2 regimens).

Overall survival (OS) at 5 years was 66% for MOPP, 73% for ABVD, and 75% for MOPP-ABVD (P = .28 for the comparison between MOPP and the doxorubicin regimens). These results, demonstrating a failure-free survival advantage but no OS difference for ABVD over MOPP, did not change after a median follow-up of 14 years. Because of its better toxicity profile compared with MOPP (lesser bone marrow suppression and long-term myelotoxicity and minimal effect on fertility), ABVD has become the de facto standard chemotherapeutic regimen used to treat cHL in the United States.

Early-Stage cHL
Patients with early-stage cHL have an excellent prognosis, with very high cure rates of >90%. In past series, these patients were more likely to die from long-term treatment-related complications than from lymphoma itself. Therefore, the focus of more recent trials has been to minimize the long-term risks of curative-intent chemotherapy and radiation. Higher doses of radiation and extended fields of treatment were associated with long-term cardiopulmonary toxicities and increased rates of breast cancer in women. The goal of combined-modality therapy (incorporating chemotherapy with radiation) has been to minimize doses of radiotherapy and substitute with combination chemotherapy, thereby preserving efficacy while minimizing toxicity.

Early trials of combined-modality therapy used the MOPP regimen—a Danish study in patients with supra-diaphragmatic, stage I and II HL compared total nodal irradiation with mantle-field radiation followed by 6 cycles of MOPP and showed a significant reduction in treatment failures with the addition of combination chemotherapy. The 1500 patient European Organization for Research and Treatment of Cancer-Groupe d’Etudes des Lymphomes de l’Adulte (EORTC-GELA) H8-F trial compared 3 cycles of MOPP combined with doxorubicin, bleomycin, and vinblastine (ABV) plus involved-field radiotherapy versus subtotal nodal radiotherapy alone—the 5-year event-free survival rate was significantly higher for the combined-modality arm at 98% versus 74%. The 10-year OS estimates were 97% and 92%, respectively (P = .001), definitively establishing combination therapy as the standard of care for early-stage, favorable-risk patients.

The German HD10 trial looked into further de-escalation of treatment for favorable-risk disease, comparing 4 treatment groups that received a combination chemotherapy regimen of 2 different intensities followed by involved-field radiation therapy at 2 different dose levels. In total, 1370 patients with newly diagnosed, early-stage cHL who had a favorable prognosis were randomized to receive either 2 or 4 cycles of ABVD followed by 20 or 30 gray (Gy) of involved-field radiation therapy. There was no significant difference between any of the 4 groups in terms of treatment failure or OS, whereas adverse events and acute toxic effects of treatment were most common in the patients who received 4 cycles of ABVD and 30 Gy of radiation. Therefore, 2 cycles of ABVD followed by 20 Gy of involved-field radiation is currently the optimal approach to deliver combined-modality treatment. Further attempts to de-escalate chemotherapy in favorable-risk patients by omitting dacarbazine and/or bleomycin have not been successful. The German HD13 trial demonstrated that dacarbazine could be omitted from ABVD without a substantial loss of efficacy, and dropping bleomycin did not meet a predefined noninferiority margin.

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) HD.6 trial compared 4 to 6 cycles of
ABVD with subtotal nodal radiation therapy in patients with early-stage cHL. In the favorable-risk cohort, both treatment approaches had identical freedom from disease progression and OS (98%) at the 12-year mark. Therefore, a radiation-free approach is feasible for patients with early-stage, favorable-risk HL who have disease at sites vulnerable to late radiation toxicities, such as near the breast and heart.

More modern approaches have attempted to use interim PET to define subgroups of patients who would benefit from the omission of radiotherapy after short-duration ABVD. The EORTC H10 trial investigated the omission of involved-node radiotherapy versus combined-modality therapy in patients who attained a negative PET scan after 2 cycles of ABVD, but the trial had to be stopped early because of increased rates of progression in the chemotherapy-only arm. The RAPID trial randomized patients who had negative PET scans after 3 cycles of ABVD to receive either consolidation involved-field radiotherapy or no further treatment. This was a noninferiority study that sought to demonstrate a 3-year progression-free survival (PFS) difference less than 7% between the 2 groups, but it could not, and the difference in the absolute risk was −3.8 percentage points (95% CI, −8.8 to 1.3 percentage points). The ABVD-only group had a 3-year PFS of 90.8%; therefore, the contribution of radiotherapy was small but statistically not insignificant in PET-negative patients. Therefore, optimal therapy in this group of patients with an overall excellent prognosis should be individualized, keeping in mind the patient’s age, sex, and comorbidities.

Early-Stage cHL With Unfavorable Prognostic Factors

Unfavorable risk factors are defined differently across the world by various cooperative groups. This has made comparisons across countries (and continents) challenging, but they incorporate criteria, such as an elevated erythrocyte sedimentation rate, the presence of B symptoms, an increased number of involved nodal sites, and tumor bulk (outlined in Table 1). The EORTC classifies age 50 years and older as unfavorable, whereas the German Hodgkin Study Group (GHSG) classifies any extranodal extension from an involved lymph node as poor risk.

The EORTC-GELA H8-U trial demonstrated identical 5-year event-free survival and 10-year OS for 3 approaches of combined-modality therapy intensity—4 cycles of MOPP-ABV chemotherapy and involved-field radiotherapy were equivalent to 6 cycles of chemotherapy and subtotal nodal radiotherapy. The shorter and less toxic regimen (4 cycles of chemotherapy with involved-field radiotherapy) has since become the standard of care for patients with unfavorable-risk cHL.

The GHSG conducted HD11 in a 2 × 2 design to compare 4 cycles of ABVD versus a more intense regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone [BEACOPP]) in combination with 20 Gy versus 30 Gy of involved-field radiotherapy. BEACOPP did not improve outcomes over ABVD, but the trial did help establish the importance of radiation dose (30 Gy was superior to 20 Gy) when used in combination with ABVD in unfavorable-risk patients. Further chemotherapy dose intensification using 2 cycles of escalated BEACOPP in the HD14 trial improved upon the 5-year PFS by 6.2% compared with combined-modality therapy using 4 cycles of ABVD but was associated with more acute toxicities and no difference in OS.

Radiation-sparing approaches have been studied less, but may have a role in patients who have early-stage nonbulky disease. The NCIC CTG-Eastern Cooperative Oncology Group HD.6 trial compared 4 to 6 cycles (depending on rapidity of response) of ABVD versus 2 cycles of ABVD plus extended-field radiotherapy. In patients who had nonbulky, unfavorable-risk disease, 12-year survival was superior in the chemotherapy-alone arm (94% vs 87%; hazard ratio [HR], 0.05 [P = .04]) despite a lower 12-year freedom from progressive disease (87% vs 92%; HR, 1.91 [P = .05]). The poorer OS in the combination arm, despite higher cHL cure rates, was attributed to higher treatment-related deaths on the combined-modality arm.

However, trials like HD.6 in patients with early-stage, unfavorable-risk cHL have not been optimal, having used older radiation techniques with extended fields rather than modern, involved-site radiation therapy, which greatly limits exposure to surrounding normal tissues (the major cause of long-term toxicity). In select patients with nonbulky disease, skipping radiation likely results in short-term loss of benefit but might be beneficial by limiting long-term toxicities.

Advanced cHL

Advanced cHL is treated mainly with combination chemotherapy. The evolution of modern cytotoxic combination regimens is outlined in the introduction to this section and has established ABVD as the primary regimen for the treatment of advanced cHL (Fig. 3).

The group at Stanford University developed a combined-modality approach—the Stanford V regimen—using reduced doses of doxorubicin and bleomycin (aimed at minimizing cardiac and pulmonary toxicity) delivered over a shorter course of 12 weeks, but this required the addition of irradiation to sites of disease >5 cm in size at diagnosis and for macroscopic splenic involvement. Multiple randomized trials have produced mostly equivalent response rates, PFS, and OS when Stanford V has been compared with ABVD. It remains an option in which limiting the
duration of chemotherapy or reducing anthracycline/bleomycin exposure takes precedence over the potential additive toxicity from irradiation.

The GHSG pioneered an intensified 7-drug combination of escalated BEACOPP (eBEACOPP) in an attempt to improve upon ABVD. Multiple trials have compared eBEACOPP with ABVD and mostly have demonstrated an improved response rate and a PFS benefit without leading to a significant OS benefit.51,52

In an Italian trial comparing eBEACOPP versus ABVD, with salvage therapy planned upon treatment failure, the estimated 7-year rate of freedom from first progression was 85% in the eBEACOPP group compared with 73% in the ABVD group (P = .004). Severe toxicities were much lower in the ABVD group compared with the eBEACOPP group (43% vs 81% with hematologic toxic effects [P < .001]; and 7% vs 19% with nonhematologic toxic effects, including severe infections and mucositis [P = .001]). OS was no different in the 2 groups because of effective second-line salvage treatment, comprising an ifosfamide-containing combination for reinduction and high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) for consolidation. eBEACOPP exposes 7 of 8 patients to an unnecessarily higher risk of toxicities, because they likely would be cured with ABVD.53

A recently updated Cochrane meta-analysis in 2017 included 5 large, randomized controlled trials comparing eBEACOPP versus ABVD for patients with early unfavorable or advanced stage cHL in which a significant PFS benefit (HR, 0.54; 95% CI, 0.45-0.64) and a small but statistically significant OS benefit (HR, 0.74; 95% CI, 0.57-0.97) were demonstrated.54 This came at the cost of increased toxicity; of particular concern to the young demographic of patients who develop cHL is the 50% infertility rate in women and 90% azoospermia in men who receive treatment with eBEACOPP.55,56 Therefore, the adoption of eBEACOPP has been limited outside of Germany. ABVD is the most commonly used regimen for advanced cHL in the United States.

The field of advanced cHL treatment has moved from using higher doses and intensity of cytotoxic agents to a risk-adapted approach. Gallamini et al showed that an interim FDG PET-CT done after 2 cycles of chemotherapy was highly prognostic—patients with a positive PET had a PFS of 12.8% at the 2-year mark, whereas those with a CR had a 95% PFS.57 This finding shifted the focus to de-escalating therapy for interim PET-negative patients and dose intensification for those with positive scans.

The Risk-Adapted Therapy in Hodgkin Lymphoma (RATHL) study enrolled 1200 patients with advanced cHL, all of whom received 2 cycles of ABVD followed by an interim PET-CT scan. Those who had a negative interim PET scan (84% of patients enrolled) were randomized to either continue ABVD or omit bleomycin for cycles 3 through 6 (the AVD group). The 3-year PFS (85%) and OS (97%) were identical in both groups, and patients on the AVD arm had lower rates of febrile neutropenia and lung toxicity.

In contrast, the 16% of patients who had a positive interim PET scans had dose intensification of therapy with a BEACOPP-based regimen, and most (74.4%) were able to achieve PET negativity on subsequent imaging. Patients in this poor-risk group had a 3-year PFS of 67.5%, which was much higher than what was seen in past experiences with the continuation of ABVD after a positive interim PET. This strategy spares patients who have an excellent prognosis from excess treatment toxicities while reserving more intensive chemotherapy regimens for patients who are likely to benefit.58

FIGURE 3. (A) Pretreatment Positron Emission Tomography/Computed Tomography Scan. Image from a patient with stage IVB Hodgkin lymphoma revealed bulky mediastinal disease; neck, axillary, and abdominal adenopathy; and splenic involvement. (B) After 6 months of chemotherapy, the post-treatment positron emission tomography/computed tomography scan revealed complete metabolic remission with resolution of all positron emission tomography avidity and adenopathy.
Overall, 32.1% of patients enrolled in the study had bulky disease at presentation, and this finding was not prognostic for patients who had a negative interim PET. Only 6.5% of patients in this trial received consolidative radiation to sites of bulky disease, suggesting that omitting radiotherapy would be reasonable in those with a negative interim PET scan.

**Treatment of Relapsed/Refractory cHL**

Most patients with cHL are cured by first-line therapy, but significant percentages of patients (especially those with advanced cHL) relapse or have primary refractory disease despite advances in combination chemoradiotherapy and risk-adapted treatment escalation. Patients with primary refractory disease (ie, those who do not achieve remission at the end of treatment) and patients who relapse less than 1 year from primary treatment have a worse prognosis in this group.

Salvage high-dose combination chemotherapy followed by autologous hematopoietic stem cell transplantation (auto-HSCT) in patients who are responding to treatment has produced the best long-term outcomes and potentially could cure about 50% of patients with relapsed cHL. In a 141-patient, retrospective analysis of patients with relapsed/refractory cHL who received treatment with consolidative auto-HSCT, at a median follow-up of 6.3 years (range, 1-20 years), the probability of PFS at 5 and 10 years was 48% (95% CI, 39%-57%) and 45% (95% CI, 36%-54%), respectively, and the probability of OS was 53% (95% CI, 44%-62%) and 47% (95% CI, 37%-57%), respectively.

Two separate randomized trials have demonstrated the benefit of high-dose therapy with autologous stem cell rescue compared with chemotherapy alone. The British National Lymphoma Investigation group compared high-dose chemotherapy (BEAM) plus autologous bone marrow transplantation versus the same drugs at lower doses, which did not require bone-marrow rescue (mini-BEAM), in patients with relapsed HL. PFS differed significantly in favor of BEAM plus autologous bone marrow transplantation (P = .005). A similar study by the GHSG started salvage with 2 cycles of dexmethylasone plus BEAM (Dexa-BEAM) and either 2 additional courses of Dexa-BEAM or high-dose BEAM with autologous stem cell rescue. Among patients with chemosensitive disease (complete or partial responders), freedom from treatment failure at 3 years was significantly better for those who received BEAM-HSCT (55%) than for those who received Dexa-BEAM (34%; P = .019). A 2013 Cochrane review reported a significant PFS benefit from the addition of auto-HSCT to conventional chemotherapy, but there was only a nonsignificantly positive difference regarding OS.

Other combination chemotherapeutic salvage regimens are more favorable to outpatient administration with a gentler toxicity profile and include drugs that have not been used as a part of frontline therapy, such as Ifosfamide (ICE [Ifosfamide, carboplatin, and etoposide]) or Gemcitabine (GDP [gemcitabine, dexamethasone, and cisplatin]). Patients with relapsed cHL who do not respond to salvage chemotherapy (chemoresistant) have significantly worse outcomes and should be candidates for novel approaches using antibody–drug conjugates or immunotherapy.

**Antibody-Drug Conjugate**

A characteristic of cHL is the universal expression of the receptor CD30 on HRS cells. Monoclonal antibodies, like the anti-CD20 antibody rituximab, have played a significant role in increasing cure rates for patients with NHL. Arming antibodies with highly potent toxic agents for selective intracellular release provides both targeting and delivery of doses of cytotoxic therapy that would not be possible if systemically given. Brentuximab vedotin (BV) is an antibody-drug conjugate containing the potent antimitotic drug monomethylauristatin E, which is linked to an anti-CD30 monoclonal antibody through a cleavable dipeptide linker. The linker undergoes proteolysis in lysosomes inside the CD30-positive cell, and free monomethylauristatin E is released. Intracellular concentrations of released drug are high over a prolonged time period, yet the amount of effluxed drug is also sufficient to exert bystander activity on surrounding CD30 antigen-negative cells.

In a pivotal phase 2 trial in patients with relapsed/refractory cHL after failed auto-HSCT, BV had an overall response rate of 75% with a CR rate of 34%. Five-year follow-up showed an OS of 41% and a PFS rate of 22%, but patients who achieved a CR to BV (n = 34) had estimated OS and PFS rates of 64% (95% CI, 48%-80%) and 52% (95% CI, 34%-69%), respectively. Of the 34 patients who had a CR, 6 underwent a consolidative allo-SCT with estimated 5-year PFS and OS rates of 67% and 83%, respectively. The other 28 nontransplantation patients who attained a CR had estimated 5-year PFS and OS rates of 48% (95% CI, 28%-68%) and 60% (95% CI, 41%-78%), respectively. Overall, 9% of all enrolled patients remained in sustained CR without receiving any further anticancer therapy after treatment with BV (given by intravenous infusion once every 3 weeks for up to 16 cycles), indicating that a limited course of treatment with BV could be curative even in a very hard-to-treat population of patients with relapsed/refractory cHL. For elderly patients and those with medical comorbidities who are not candidates for multiagent salvage chemotherapy and autologous stem cell transplantation, BV can be an effective yet well tolerated therapy.

Neuropathy is the main nonhematologic toxicity of BV and is managed by dose reduction or drug holiday. Most patients experience either resolution or improvement in
symptoms a year after the completion of therapy, and improvement can take several months.67

About one-half of patients with relapsed cHL after first-line treatment can be cured with salvage chemotherapy and autologous stem cell transplantation, but those who have primary refractory cHL (not achieving remission) and patients who relapse early after the completion of first-line therapy do much worse. The objective of the AETHERA trial was to determine whether early BV consolidation after autologous stem cell transplantation could prevent relapse. Patients with unfavorable-risk relapsed or primary refractory cHL who had undergone autologous stem cell transplantation were randomly assigned to receive 16 cycles of either BV or placebo. Median PFS was significantly improved for patients in the BV group at 42.9 months compared with those in the placebo group at 24.1 month, with a PFS HR of 0.57 (95% CI, 0.40–0.81).68 OS was no different between the 2 arms, a result likely confounded by the 85% of patients in the placebo group who received BV after progression. Across both arms, the 3-year rate of OS was >80%, a testament to the activity of BV as both consolidation and salvage therapy in patients at high risk of relapse after autologous stem cell transplantation.

BV is being investigated in earlier lines of therapy for cHL. A phase 1 study in patients with advanced cHL who received first-line therapy versus BV in combination with a standard (ABVD) or modified-standard (AVD) regimen demonstrated unacceptably high pulmonary toxicity rates (44%) in the BV plus ABVD arm. The lung injury rates were much higher compared with past experiences with ABVD; BV is thought to potentiate bleomycin-mediated lung damage, and the 2 agents should not be used together.69 BV with AVD was well tolerated without unexpected side effects and no pulmonary toxicities, making this a promising regimen for earlier lines of therapy, especially for patients with preexisting pulmonary compromise. A frontline trial in patients with advanced cHL comparing BV plus AVD versus ABVD has been completed and is awaiting publication.

Immunotherapy

Combination chemotherapy is able to cure most patients with cHL; however, for those who have disease that did not respond to treatment (refractory cHL) or that returned soon after completion of therapy (relapsed cHL), immunotherapy has drastically changed the vista. cHL tumors are almost unique in being composed of a tiny fraction of cancer cells (HRS cells) in a sea of dysfunctional, reactive immunologic cells (lymphocytes, plasma cells, macrophages, etc) that comprise most of the tumor mass. The neoplastic HRS cells secrete a variety of cytokines and chemokines to manipulate the microenvironment and evade immune attack.70 One of the pathways involved in the functional impairment of T cells observed in tumor immune evasion is the PD-1-PD-1 ligand (PD-L1) signaling system. Tumor cells expressing PD-1 ligand on their surface engage the PD-1 receptor on T cells and inhibit T-cell activation and proliferation.

PD-1 expression is markedly elevated in tumor-infiltrating T cells of cHL, and PD-L1 expression is high in the malignant HRS cells.71 EBV infection also induces PD-L1 expression in cHL.72 Most cHL specimens show chromosome 9p24.1 alterations (56% show copy gain; 5% polysomy and 36% amplification), which result in overexpression of the PD-1 ligands and promote their induction through Janus kinase-signal transducer and activator of transcription signaling.73 All of these factors made PD-1/PD-L1 a promising pathway to target therapeutically with immune checkpoint blockade.

In a heavily pretreated population of patients with cHL (of whom 78% relapsed after autologous stem cell transplantation, and 78% relapsed after BV), an objective response to the novel PD-1 antibody nivolumab was observed in 87% of patients, including 17% of patients in complete remission. Responses were also durable, with an 86% PFS rate at 24 weeks.74 In a similar cohort of heavily pretreated patients with cHL, nivolumab demonstrated an objective response in 53 of 80 patients (66.3%, 95% CI, 54.8%–76.4%). In addition to being effective at shrinking cHL tumors, nivolumab was well tolerated, with the most common drug-related adverse events including fatigue, infusion-related reactions, and rash.75

Pembrolizumab, a PD-1 inhibitor, was studied in a large trial of 210 adult patients who had refractory or relapsed cHL after autologous stem cell transplantation (129 patients) and/or BV (175 patients) and had received a median of 4 prior systemic therapies. The overall response rate was 69% (95% CI, 62%–75%); partial responses were observed in 47% of patients, and 22% had CRs. The estimated median response duration was 11.1 months.76

Checkpoint inhibition is not associated with the toxicities of traditional cytotoxic therapy, such as nausea, vomiting, hair loss, etc, but comes with a risk of several autoimmune side effects. These adverse reactions are related to a hyperactive T-cell response, resulting in the generation of high levels of CD4 T-helper cell cytokines or increased migration of cytolytic CD8 T cells within normal tissues.77 Skin rash is the most common immune-mediated side effect of checkpoint inhibition and presents most commonly with a maculopapular rash. More severe reactions, including Sweet syndrome, Stevens Johnson syndrome, and toxic epidermal necrolysis, have been reported.78 Pneumonitis affected about 5% of patients with lung cancer who were treated with PD-1 inhibitors, but data from patients with cHL are lacking.79 Fulminant myocarditis has been reported with combination
immune checkpoint blockade and both PD-1 blockers discussed above. Diarrhea/colitis and endocrine toxicities, such as hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, and adrenal insufficiency, have been widely described with checkpoint blockade. Clinically significant immune-related adverse events are managed by withholding anti–PD-1 treatment and may require steroids and other immunosuppressive medications when severe.

Checkpoint inhibitors may be associated with imaging findings during treatment suggestive of progressive disease despite evidence of clinical benefit. Immune-mediated tumor flare or pseudoprogression can lead to patients being taken off treatment too early. To address this issue in the context of lymphoma immunomodulatory therapy, modified response criteria have been developed, including an indeterminate response to identify lesions until they are confirmed as pseudoprogression or true progressive disease on subsequent imaging (Fig. 4).

Allogeneic hematopoietic stem cell transplantation (allo-HCT) can be curative in relapsed/refractory cHL, but relapse rates remain as high as 40% even with alternate donor sources, such as human leukocyte antigen (HLA)-haploidentical allo-HCT. Early trials of nivolumab and pembrolizumab in cHL excluded patients who had a previous history of allo-HCT because of concern about potentiation or reactivation of graft-versus-host disease (GVHD) by PD-1 inhibition. A French study retrospectively assessed the efficacy and toxicity of nivolumab in 20 patients with cHL who had relapsed after allo-HCT. The overall response rate was an impressive 95%, with 42% CRs, and, at a median follow-up of 1 year, the median PFS and OS had not been reached.

Nivolumab-induced GVHD occurred in 6 patients (30%) within 1 week of the first dose, prompting discontinuation after a single infusion. All of these patients had a history of prior acute GVHD. No nivolumab-induced GVHD was observed in patients who had a prior history of chronic GVHD but no prior acute GVHD. The time between allo-HCT and nivolumab treatment was significantly shorter in patients who presented with nivolumab-induced GVHD (median, 8.5 months [range, 2–19 months] vs 28.5 months [range, 7–111 months]; P = .0082). Another US multicenter, retrospective study reported a 77% response rate for PD-1 blockade after allo-HCT, but just over one-half of patients (55%) developed treatment-emergent GVHD after the initiation of anti–PD-1, usually after 1 or 2 doses of checkpoint blockade. In conclusion, PD-1 blockade in patients with relapsed cHL who undergo allo-HCT appears to be highly efficacious but is frequently complicated by rapid onset of severe and treatment-refractory GVHD. Therefore, checkpoint inhibition might be an alternative to donor lymphocyte infusion for select patients with relapsed/refractory cHL who need a tumor response, but such treatment is complicated by high rates of GVHD.

Another subject of active debate is the safety of allo-HCT in patients after PD-1 blockade therapy. An international retrospective analysis of 39 patients with lymphoma who received prior treatment with a PD-1 inhibitor before allo-HCT showed 1-year cumulative incidences of grade 2 through 4 and grade 3 and 4 acute GVHD of 44% and 23%, respectively, whereas the 1-year incidence of chronic GVHD was 41%. All those who were treated concurrently with ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody, and a PD-1 inhibitor developed acute GVHD, including a fatal case of grade 4, acute GVHD. An atypical, noninfectious febrile syndrome was reported in 7 patients; this developed shortly post-transplant and required prolonged courses of steroid therapy. Despite these hurdles, the 1-year OS and PFS rates were 89% (95% CI, 74%–96%) and 76% (95% CI, 56%–87%), respectively, indicating that allo-HSCT is feasible in patients who have received prior PD-1 blockade.

The excellent tolerability, high response rate, and potential durability of response to immunotherapy in patients with cHL hold great promise. Newer trials are looking to advance immuno-oncologics into earlier lines of treatment and in novel combinations with BV for a chemo-free approach to treating relapsed/refractory cHL.

**Allogeneic Stem Cell Transplantation**

Allo-HCT can produce long-term disease control via the graft-versus-lymphoma effect, but its use was limited in the
past due to a lack of suitable donors and the acute morbidity and mortality in the peri-transplant period.90 Major changes in transplant technology in the last 15 years have helped drive improvement in outcomes with allo-HCT. A meta-analysis of allo-HCT studies that included 1850 patients who received treatment for HL reported that 3-year relapse-free survival was 31% (range, 25%-37%), and 3-year OS was 50% (range, 41%–58%). An accrual initiation year of 2000 or later was associated with 5% to 10% lower nonrelapse mortality and relapse rates and 15% to 20% higher relapse-free survival and OS.91

The advent of reduced-intensity conditioning
Myeloablative preparative regimens use high doses of chemotherapy and radiation pretransplantation to get maximum tumor kill and induce immunosuppression, which enables engraftment of donor hematopoietic stem cells. However, myeloablation is associated with higher short-term toxicities and worse nonrelapse mortality. Nonmyeloablative or reduced-intensity conditioning (RIC) regimens use lower doses of chemoradiotherapy, have lower early post-transplantation morbidity and mortality, and rely mainly on the immunological properties of the graft to combat lymphoma. The graft-versus-lymphoma effect, which is responsible for long-term disease control, does not depend on the intensity of the preparative regimen.90,92

A retrospective European study in patients with relapsed/refractory HL who underwent allo-HCT found improved nonrelapse mortality (HR, 2.85; 95% CI, 1.62-5.02) and OS (HR, 2.05; 95% CI, 1.27-3.29 [P = .04]) in patients who received RIC regimens compared with those who received myeloablative conditioning.93

The use of alternate donor sources
Less than one-third of patients have matched-sibling donors (MSDs) for allo-HCT, and a search for a suitable HLA-matched unrelated donor through the National Marrow Donor Program can take several months. Alternate donor sources, such as umbilical cord blood (UCB) and HLA-haploidentical donors, have overcome most problems related to donor availability in allo-HCT.

In a retrospective case-series of RIC allo-HCT, equivalent outcomes were reported using either unrelated UCB donors or MSDs for patients with advanced HL with comparable 2-year PFS rates of 25% for UCB and 20% for MSDs, respectively.94 A single unit of UCB might not have adequate hematopoietic progenitors, leading to slower engraftment and higher risk of graft failure. The use of 2 UCB units together (double UCB transplantation) in RIC allo-HSCT can mitigate some of these risks and has been shown to be feasible and efficacious (5-year PFS, 31.3%) in a heavily pretreated cohort of patients with HL.95

Almost all patients have a first-degree relative (eg, either parent or progeny) who is identical for one HLA haplotype who could serve as a haploidentical donor. Modern immunosuppressive regimens using post-transplantation cyclophosphamide are able to effectively minimize the rates of GVHD in patients who undergo a haploidentical allo-HSCT. A multicenter, retrospective review of RIC allo-HCST for 90 patients with relapsed or refractory HL compared outcomes among recipients of transplants from HLA-matched related (n538), unrelated (n524), or HLA-haploidentical related (n528) donors. Two-year OS and PFS were 53% and 23%, respectively, for recipients of transplants from HLA-matched related donors; 58% and 29%, respectively, with unrelated transplants; and 58% and 51%, respectively, with HLA-haploidentical related transplants. The risks of relapse were lower in the HLA-haploidentical recipients compared with the other 2 groups, and neither acute nor chronic GVHD rates were increased.86

Nodular Lymphocyte-Predominant HL
NLP HL comprises a small percentage (about 5%) of the total number of patients diagnosed with HL. It is generally a much more indolent lymphoma, is usually asymptomatic, and is always negative for EBV. Unlike cHL, in which HRS cells are CD15-positive, CD30-positive, and CD45 negative, the malignant cells in NLP HL are CD15-negative, CD30-negative, CD45-positive germinal center B cells and invariably express CD20. The malignant cells exhibit a nodular growth pattern and popcorn-like, lymphocytic-histiocytic malignant cells without much fibrosis. There is a striking predilection for males, who make up approximately 75% of all patients diagnosed with the disease, and a strong familial risk (the standardized incidence ratio in first-degree relatives of patients was 19 in a Finnish study).96,97 Almost 80% of patients present with stage I or II lymphadenopathy at diagnosis and have an excellent long-term prognosis.17

In contrast to cHL, the treatment of NLP HL is not clearly defined; older studies are confounded by the inclusion of NLP HL with cHL, although the natural history of both diseases is very different. There are no randomized controlled trials of NLP HL treatment, and treatment recommendations are based mostly on case series.

Early-stage NLP HL

- Complete surgical excision without adjuvant therapy has exhibited excellent efficacy in pediatric patients with early-stage NLP HL: a Children’s Oncology Group study demonstrated a 5-year event-free survival of greater than 75%.98,99
- Radiation therapy alone is potentially curative in early-stage NLP HL. An Australian study showed that 15-year
freedom from progression was 82% and OS was 83% among patients who received local radiation.\textsuperscript{100} Patients with stage IA NLPHL who were treated within GHSG studies between 1988 and 2009 received combined-modality treatment (n = 72), extended-field radiotherapy (n = 49), involved-field radiotherapy (n = 108), or 4 weekly standard doses of rituximab (n = 27). At 8 years, PFS and OS rates were 91.9% and 99.0%, respectively, for involved-field radiotherapy, with identical tumor control in all treatment arms, including radiation.\textsuperscript{101} Current guidelines from the International Lymphoma Radiation Oncology group recommend involved lymph node or involved site radiation therapy using 30 to 36 Gy to treat early-stage LPHL.\textsuperscript{102}

**Advanced stage NLPHL**

Patients who have advanced-stage (III/IV) NLPHL have a worse prognosis than those who have early-stage NLPHL, with systemic symptoms and relapses over an extended period. The prognosis for patients with advanced NLPHL is also significantly worse than that for patients with advanced cHL and often resembles the natural history of low-grade NHL.\textsuperscript{103} A multicenter, retrospective analysis in the 1990s (before the advent of monoclonal antibody-based therapy) reported that virtually all patients responded to first-line chemotherapy, but about 38% of those with stage III disease and 76% of those with stage IV disease relapsed over an 8-year period after the completion of chemotherapy.\textsuperscript{18}

A particular concern in NLPHL is the increased risk of transformation to aggressive, diffuse large B-cell lymphoma, which is a type of aggressive NHL. In a retrospective study at the Mayo Clinic, the transformation rate was 7.6% after a median follow-up of 16 years (transformation rate, 0.74 per 100 patient-years), but the British Columbia Cancer Agency reported higher actuarial risk of transformation of 7% and 30% at 10 and 20 years, respectively.\textsuperscript{104,105} Both studies identified splenic involvement as a significant risk factor for transformation.

- **Rituximab** is a monoclonal antibody targeting CD20 that has revolutionized the treatment of CD20-positive B-cell NHL. It has a favorable adverse-effect profile without the standard toxicities associated with cytotoxic agents. In patients with newly diagnosed or relapsed NLPHL who received treatment once weekly, a 4 week course of rituximab had a 100% response rate (CR, 67%; partial response, 33%), but most patients relapsed (estimated 5-year PFS, 39.1%). When followed by maintenance rituximab (once every 6 months for 2 years), the estimated 5-year PFS was extended to 58.9%.\textsuperscript{106} These results are similar to other reports of the efficacy of rituximab in this disease.\textsuperscript{107,108}

- Multiagent combinations like ABVD and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in combination with rituximab are the most commonly used chemotherapeutic regimens for the treatment of symptomatic patients with advanced, LPHL in the United States. A retrospective review from The University of Texas MD Anderson Cancer Center of 59 patients with advanced NLPHL who were treated with combined rituximab and CHOP demonstrated a CR rate of 89% and an estimated 5-year and 10-year PFS of 89% and 60%, respectively, without any transformation.\textsuperscript{109} Although prospective data for this approach are limited because of the rarity of patients who present with this disease in an advanced stage, we follow the National Comprehensive Cancer Network consensus guidelines in treating this disease with rituximab-based combination chemotherapy, a strategy with extensive data in patients with NHL.\textsuperscript{110}

**Survivorship**

With current treatment advancements, approximately 90% of all patients diagnosed with HL will be long-term survivors. HL is also a disease of the young, most frequently seen in the group ages 20 to 34 years; therefore, patients could require decades of monitoring before the full spectrum of treatment toxicity could potentially manifest as a competing cause of morbidity and mortality. A Dutch study of long-term cause-specific mortality of patients treated for HL found a continuing increase in the relative risk of death from all causes other than HL, which was 6.8 times that of the general population, and still amounted to 5.1 after more than 30 years.\textsuperscript{111} The available long-term toxicity data are not necessarily directly applicable to patients who currently receive HL treatment—older regimens, such as MOPP chemotherapy, mantle-field radiation, and subtotal nodal radiation, are rarely if ever used anymore but can be useful in assessing the potential side effects of modern chemoradiotherapy regimens.

A prime example of having to balance out cure versus the risks of delayed treatment toxicity is the NCIC CTG–Eastern Cooperative Oncology Group HD.6 trial of patients with early-stage, unfavorable-risk disease. In that trial, long-term survival was superior in the chemotherapy-alone arm (94% vs 87%) despite a lower freedom from progressive disease (87% vs 92%) in the combined-modality arm primarily because of higher delayed combined-modality treatment-related deaths.\textsuperscript{44}

**Second Malignancies**

Multiple studies have reported an increased risk for second (and multiple) cancers after treatment for HL—both hematologic neoplasms and solid tumors together form the largest cause of mortality in long-term survivors of HL.\textsuperscript{111,112}
Rates of acute myeloid leukemia declined significantly starting in the mid-1980s, with ABVD replacing the alkylator-heavy MOPP chemotherapy regimen, but remain much higher than in the general population. HL survivors are also at 13 times higher risk of developing a second primary NHL.113,114

Second primary solid tumors form the major burden of secondary cancers, with increased long-term risk for cancers of the oropharynx, esophagus, stomach, colon, pancreas, lung, breast, urinary bladder, and thyroid and for mesothelioma, melanoma, and sarcoma. A Dutch study with 40 years of follow-up estimated that the standardized incidence ratio for any solid cancer was 4.2, with an absolute excess risk of 100 cancers per 10,000 person-years and a 30-year cumulative incidence of 29%. Despite therapeutic advances in HL treatment, this increased cumulative incidence of second solid cancers did not differ between patients treated in the 1960s and those treated in the 1990s.114 Lung cancer accounts for a substantial number of these cases (25 cases per 10,000 person-years), and HL survivors experience significantly inferior stage-specific OS compared with patients who have de novo lung cancer.115

The risk of female breast cancer secondary to radiotherapy is particularly high in those who received radiation when younger than 30 years of age, and the increase remains for decades after completion of radiotherapy. In a study of women who received mantle irradiation for HL, the relative risk of breast carcinoma was 56.0 for those age 19 years or younger at the time of treatment, 7.0 for those ages 20 to 29 years, and 0.9 for those 30 years and older.116 Other studies have reproduced similar results, confirming that breast tissue is highly susceptible to ionizing radiation in younger females, necessitating long-term surveillance.117 With newer radiation techniques and lower dose exposure to breast tissue, the rates of breast cancer are hypothesized to be lower than with mantle irradiation.118 The American Cancer Society and other organizational guidelines recommend screening MRI as a useful adjunct to routine mammography for women treated with mediastinal radiation, who have a 20% to 25% or greater lifetime risk of breast cancer.119,120

Nonmalignant, Systemic Side Effects

Patients with HL are susceptible to nonischemic cardiomyopathy from anthracycline chemotherapy mediated by oxidative stress and apoptosis. Anthracyclines like doxorubicin form the backbone of almost all modern chemotherapeutic regimens for HL and can cause a dose-dependent, systolic dysfunction, especially once the cumulative dose exceeds 400 mg/m². Delayed late cardiotoxicity can present as overt heart failure or asymptomatic left ventricular dysfunction several years after the completion of chemotherapy.121

HL survivors are also at risk for coronary heart disease from radiation exposure. A Dutch study revealed that the risk

FIGURE 5. Timeline of Landmark Developments in Hodgkin Lymphoma Over the Last Decade. Allo-HCT indicates allogeneic hematopoietic stem cell transplantation; cHL, classic Hodgkin lymphoma; HD10, a German Hodgkin Study Group trial; PD-1, programmed death 1; PET/CT, positron emission tomography/computed tomography. Italicized acronyms indicate the journal of publication (BBMT indicates Biology of Blood and Marrow Transplantation; NEJM, The New England Journal of Medicine; JCO, The Journal of Clinical Oncology).
of coronary disease increased linearly with increasing mean heart dose (excess relative risk per gray, 7.4%), with a median interval of 19 years between a diagnosis of HL and coronary heart disease. However, most patients in that retrospective study were treated with older radiation techniques; contemporary radiotherapy minimizes critical organ exposure with radiation dose reduction, radiation field/volume reduction, and the use of modern radiotherapy planning and delivery.\textsuperscript{123} HL survivors are also at risk for valvular dysfunction and congestive heart failure from the cumulative effects of combined-modality therapy with anthracyclines and radiation.\textsuperscript{124}

Pulmonary toxicities can arise acutely and subacutely during treatment (bleomycin or radiation-induced pneumonitis) and may lead to chronic respiratory impairment. Patients with prior bleomycin exposure are advised against highly inspired supplemental oxygen concentrations because of anecdotal reports of late lung toxicity. Patients whose thyroids are irradiated as a part of their HL treatment are at 50% risk for thyroid disease at 20 years—mostly hypothyroidism and Graves disease.\textsuperscript{125}

Infertility

ABVD carries little to no excess risk of premature ovarian failure compared with alkylating chemotherapy (MOPP and BEACOPP), which can impair gonadal function and fertility recovery postchemotherapy.\textsuperscript{126} In patients with relapsed disease who are receiving salvage chemotherapy/high-dose therapy or allo-HCT, preservation of ovarian function and fertility is unlikely. Sperm banking, embryo cryopreservation, and oocyte freezing potentially can be used before the initiation of therapy in patients with HL who desire fertility preservation.\textsuperscript{127}

Conclusions

Treatment for HL has improved significantly since the ABVD chemotherapeutic combination was invented over 30 years ago (Fig. 5). Despite using the same ABVD regimen in most patients treated in the first line, we now have a much better understanding of disease biology and the side effects of therapy, and we have moved toward a personalized, risk-adapted approach. This approach promises to deliver low toxicities and high cure rates for lower risk patients while reserving aggressive regimens for those high-risk patients who really need them. For the minority of patients who fail first-line therapy, novel drugs like the antibody-drug conjugate BV and immunotherapies with nivolumab and pembrolizumab have produced high response rates and durability of benefit. Further research is needed to determine whether these novel drugs could make life better for both patients with HL who are undergoing treatment and for the growing cohort of HL survivors.
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