Hodgkin's Lymphoma- a Review: Future Directions in the Era of Targeted Therapy

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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 in their 20s with a small proportion of patients in their 70s. Patients usually present with supra-diaphragmatic lymphadenopathy with or without associated systemic B symptoms. Even in advanced disease, HL is highly curable with combination chemotherapy, or combined-modality treatment. Although the same doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) 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. Limited stage disease without risk factors (RFs), are frequently treated with two cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) followed by 20Gy involved-field or -site radiotherapy (IF/IS-RT). In patients with early-stage unfavorable disease, four cycles of chemotherapy are usually consolidated with 30Gy IF/IS-RT. Compared to 4xABVD, 2 cycles of escalated BEACOPP followed by 2 cycles of ABVD ("2+2") improved 5-year progression-free survival with similar 5-year overall survival. Recently, treatment strategies based on 18FDG positron emission tomography response were evaluated. PET-guided omission of RT can constitute a valid therapeutic option in patients with an increased risk of RT-associated toxicity. There are an increasing number of salvage therapies available to patients who are not cured with initial therapy. These include alternative 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.

Key words: Hodgkin lymphoma, allogeneic stem cell transplantation, antibody-drug conjugate, brentuximab, 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 a 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 centre or post germinal centre B cells led to the term Hodgkin lymphoma (HL) gaining favour.² Characteristically, the cancer cells form a minority of the tumour and are surrounded by a reactive inflammatory milieu comprising lymphocytes, eosinophils, neutrophils, histiocytes, and plasma cells. These characteristic malignant cells appear as multinucleate giant cells or large mononuclear cells are referred to as Hodgkin and Reed-Sternberg (HRS) cells and are pathognomonic of HL. It is estimated that HL accounts for approximately 10% of cases of newly diagnosed lymphoma in the United States, with the remainder are non-Hodgkin lymphoma (NHL). It accounts for about 0.5% of newly diagnosed cases of cancer in the United States and about 0.2% of all cancer deaths. Histologically, classical HL (cHL) accounting for 95% of all HL cases is distinguished from nodular lymphocyte-predominant HL (NLPHL) representing 5% of all HL cases.³

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Epidemiology and Pathogenesis

Males comprise about 56% of patients newly diagnosed with HL in 2017.⁴ The median age of diagnosis is 39 years with ages 20 to 34 years being most commonly affected. 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.⁵ The aetiology of HL is not well understood. EBV is detected in HRS cells in a majority of cHL specimens from the developing world. The risk of developing EBV-positive cHL is significantly increased (relative risk, 4.0; 95% confidence interval [95% CI], 3.4–4.5) after an episode of infectious mononucleosis.^{6,7} However, the absolute risk of developing cHL after infectious mononucleosis remains small at approximately 1 in 1000. Immunosuppression in a variety of medical conditions increases the risk of cHL.

The incidence of cHL is significantly higher in the HIV Infected population than in the general population. Most cases are EBV-positive and can occur in patients who have normal CD4 counts with a more aggressive histological phenotype.^{8–9} The incidence of cHL also increases after solid organ transplantation and in patients with a history of autoimmune conditions.¹⁰

Classification

HL is subdivided into classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL) based on morphology and immunohistochemistry.² Over 90% of cases are of cHL, whereas 10% are lymphocyte-predominant HL (LPHL). 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.¹¹

Nodular Sclerosis

Nodular sclerosis cHL (NSCHL) is the most common subtype, accounting for about 70% of cHL cases 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.¹² NSCHL has a better prognosis than other subtypes of cHL.²

Mixed Cellularity

Mixed-cellularity cHL (MCCHL) comprises 20% to 25% of cHL. 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 than in NSCHL.¹³

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.^{14,15}

Lymphocyte Depleted

Lymphocyte-depleted cHL is the rarest cHL subtype, accounting for <1% of cases. Tumour 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.

Clinical Presentation and Initial Workup

cHL is most commonly diagnosed in the group ages 20 to 34 years, 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. Other sites in descending order of frequency include splenic, axillary, abdominal, hilar, or inguino-femoral.¹⁶ Fevers, chills, night sweats, or unexplained weight loss >10% of body weight, known as B symptoms are frequent in patients with advanced or bulky disease.

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Erythrocyte sedimentation rate, can be elevated at diagnosis and can serve as a useful laboratory marker of disease response. Excisional biopsy of the involved lymph node is preferred to establish a definitive diagnosis. Fine needle aspirate is never sufficient for a new diagnosis. CCL17 (TARC) is highly expressed by the HRS cells in cHL and is being investigated in CANDEL Study as a potential biomarker of HL.¹⁷

Staging Hodgkin Lymphoma

The Ann Arbor staging system with Cotswolds modification has been in use since 1989 for initial staging. Fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) has very high sensitivity and specificity in HL. An international working group 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.¹⁸ The Lugano classification in 2014 modernized staging for lymphomas with FDG PET-CT formally incorporated into standard staging. FDG PET-CT may also supplant the utility of bone marrow biopsy in HL.¹⁹

Prognosis and risk stratification

The outlook for patients with early-stage disease (stage I–IIA) is excellent, with overall survival exceeding 90% in many trials. In advanced-stage disease, overall survival is between 75–90%. In both early-stage and advanced-stage disease, further stratification according to risk factors is often done. Early-stage disease is stratified into favourable and unfavourable by some groups according to the presence or absence of risk factors. Evidence shows that profound treatment reductions can be made in favourable early-stage disease.²⁰ In advanced stage disease, the international prognostic score known as the Hasenclever score is used to predict prognosis.

PET in Hodgkin's lymphoma

¹⁸F-FDG PET can be used in combination with CT for staging, interim assessments, end-of-treatment and follow-up surveillance. In prospective studies, ¹⁸F-FDG PET at diagnosis upstaged 13–24% more patients than did CT.^{21,22,23} The staging ¹⁸F-FDG PET

also provides a baseline scan against which subsequent scans can be compared. End-of-treatment ¹⁸F-FDG PET can be used to distinguish between fibrotic tissue and residual active disease. In a prospective study, negative end-of-treatment ¹⁸F-FDG PET had a 96% (95% CI 91–97) negative predictive value for progression or early relapse in advanced-stage disease.²⁴ Thus, in advanced-stage patients with a residual mass but a negative end-of-treatment ¹⁸F-FDG PET scan, radiotherapy could potentially be omitted.

¹⁸F-FDG PET has been adopted in the revised response criteria for lymphoma, which require a negative scan to classify a patient as in complete remission and allows residual masses if they are not ¹⁸F-FDG avid—this has been termed metabolic complete remission.²⁵ Although the negative predictive value of ¹⁸F-FDG PET is very high, the positive predictive value is less reliable, with false-positives occurring because of infection, inflammation, increased uptake of ¹⁸F-FDG in brown fat, and reactive changes after treatment. Thus, to ascertain whether relapse has occurred, histological evidence is preferable to ¹⁸F-FDG PET alone. Currently, the greatest interest is in the potential use of ¹⁸F-FDG PET for interim assessment after initial cycles of chemotherapy. The aim is to identify responders and non-responders to therapy. Response after two cycles of chemotherapy is more predictive of outcome than traditional risk stratification based on results of clinical and laboratory tests.^{26,27,28}

Treatment of Newly Diagnosed Classical Hodgkin's Lymphoma

Chemotherapy and radiation are the mainstays of cHL treatment. Before the advent of combination chemotherapy, this was invariably a fatal malignancy with a 5-year survival of less than 10%.²⁹ Advances in understanding the biology of the disease and improvement in modalities of chemotherapy and radiotherapy have improved survival every stage of cHL. 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.⁵

Early-Stage classical Hodgkin's Lymphoma (cHL)

Patients with early-stage cHL have an excellent prognosis with very high cure rates of over 90%. In past, 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 radiotherapy. The goal of combined-modality therapy has been to minimize doses of radiotherapy and substitute with combination chemotherapy, thereby preserving efficacy while minimizing toxicity. The 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, favourable-risk patients.³⁰

The German HD10 trial looked into further de-escalation of treatment for favourable-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 favourable 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 in early-stage; favourable risk cHL.³¹ Unfavourable risk factors are defined differently across the world by various cooperative groups. Chemotherapy and involved-field radiotherapy were equivalent to 6 cycles of chemotherapy and subtotal nodal radiotherapy.³² The shorter and less toxic regimen (4 cycles of chemotherapy with involved-field radiotherapy) has since become the standard of care for patients with unfavourable-risk early stage cHL. The GHSG HD11 study compared 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 unfavourable-risk patients.³³

Advanced stage classical Hodgkin's Lymphoma cHL

Advanced stage cHL is treated mainly with combination chemotherapy. 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. Multiple randomized trials have produced mostly equivalent response rates in PFS and OS when Stanford V has been compared with ABVD.^{34,35} Stanford V 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.^{36,37} 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 non-haematological toxic effects, including severe infections and mucositis [$P: 0.001$]). OS was not different in the 2 groups because of effective second-line salvage treatment.³⁸

A recently updated Cochrane meta-analysis in 2017 included 5 large, randomized controlled trials comparing eBEACOPP versus ABVD for patients with early unfavourable or advanced stage cHL in which a significant PFS benefit of (HR, 0.54; 95% CI, 0.45-0.64) and a small but statistically significant OS benefit of (HR, 0.74; 95% CI, 0.57- 0.97) were demonstrated in favour of eBEACOPP.³⁹ This came at the cost of increased toxicity; of particular concern to the young patients who develop cHL is the 50% infertility rate in women and 90% azoospermia in men who receive

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treatment with eBEACOPP.^{40,41} 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, European unions and outsides.

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.²⁶ This finding shifted the focus to deescalating 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.⁴²

Treatment of Relapsed/Refractory classical Hodgkin's Lymphoma cHL

Most patients with cHL are cured by first-line therapy, but significant percentages of patients relapse or have primary refractory disease despite advances in combination chemo radiotherapy and risk-adapted treatment escalation.^{36,41} Patients with primary refractory disease and patients who relapse less than 1 year from primary treatment have a worse prognosis in this group.⁴³ 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, retrospective analysis of 141 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.⁴⁴

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.⁴⁵ PFS differed significantly in favour of BEAM plus autologous bone marrow transplantation ($P=0.005$). A similar study by the GHSG started salvage with 2 cycles of dexamethasone plus BEAM (Dexa-BEAM) and either 2 additional courses of Dexa-BEAM or high-dose BEAM with autologous stem cell rescue. Among patients with chemo sensitive 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%; $P: 0.019$).⁴⁶ A 2013 Cochrane review reported a significant PFS benefit from the addition of auto-HSCT to conventional chemotherapy, but there was an insignificant positive difference regarding OS.⁴⁷ Patients with relapsed cHL who do not respond to salvage chemotherapy have significantly worse outcomes and should be candidates for novel approaches using antibody drugs or immunotherapy.

Immunotherapy

Antibody-Drug Conjugate: Brentuximab Vedotin

A characteristic feature of cHL is the universal expression of the receptor CD30 on HRS cells. Brentuximab vedotin (BV) is an antibody drug conjugate containing the potent antimitotic drug monomethylauristatin E, which is linked to an anti-CD30 monoclonal antibody. 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 (n534) 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 non-transplantation 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.⁴⁸ For elderly patients and those with medical comorbidities who are not candidates for multi-agent salvage chemotherapy and autologous stem cell transplantation, BV can be an effective yet well tolerated therapy. Neuropathy is the main non-hematologic toxicity of BV and is managed by dose reduction or drug holiday.

Check-Point Inhibitors

The neoplastic HRS cells secrete a variety of cytokines and chemokines to manipulate the microenvironment and evade immune attack.⁴⁹ One of the pathways involved in the functional impairment of T cells observed in tumour immune evasion is the PD-1 ligand (PD-L1) signalling system. Tumour 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 tumour infiltrating T cells of cHL, and PD-L1 expression is high in the malignant HRS cells.⁵⁰ These factors known as immune check point make PD-1/PD-L1 a promising pathway to target therapeutically with immune checkpoint blockade.

In a heavily pre-treated 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 17% of patients in complete remission. Responses were also durable, with an 86% PFS rate at 24 weeks.⁵¹ In a similar cohort of heavily pre-treated 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 tumours, Nivolumab was well tolerated, with the most common drug related adverse events including fatigue, infusion-related reactions, and rash.⁵² 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.⁵³

Skin rash is the most common immune-mediated side effect of checkpoint inhibition and presents most commonly with a maculopapular rash. Diarrhoea/colitis and endocrine toxicities such as hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, and adrenal insufficiency, have been widely described with checkpoint blockade.⁵⁴ Clinically significant immune-related adverse events are managed by withholding anti-PD-1 treatment and may require steroids and other immunosuppressive medications when severe.

Stem-cell transplantation

Autologous stem-cell transplantation

Data from randomised trials show improved progression-free survival with salvage chemotherapy followed by autologous stem-cell transplantation compared with salvage chemotherapy alone.^{45,55} The depth of response to salvage chemotherapy before autologous stem-cell transplantation is important, with improved progression-free and overall survival for patients in complete remission. Evidence shows that a negative ¹⁸F-FDG PET scan after salvage chemotherapy predicts outcome after autologous stem cell transplantation.^{56,57} Overall survival in patients with relapsed disease treated with this technique is greater than 65%, compared with 30% in refractory disease.⁵⁸

Allogeneic Stem-cell transplantation

Evidence of a graft-versus-disease effect in Hodgkin's lymphoma has resulted in increased use of reduced intensity conditioning allogeneic transplantation in patients who did not respond to standard salvage therapy; treatment-related mortality of this procedure in expert centres is roughly 20%.⁵⁹⁻⁶¹ In a donor

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versus no-donor analysis of patients who relapsed after autologous stem-cell transplantation, both progression-free (39.3% vs 14.2%) and overall survival (66% vs 42%) were significantly higher in the donor group than in the no-donor group ($p < 0.001$).⁶² Allogeneic transplantation might also be beneficial in selected high-risk patients who have not had autologous stem-cell transplantation, but precise indications are controversial.

Nodular Lymphocyte-Predominant HL

NLPHL comprises a small percentage (about 5%) of the total number of patients diagnosed with HL. It is generally a much more indolent lymphoma. Patients are usually asymptomatic and it is always negative for EBV. Unlike cHL, the malignant cells in NLPHL are CD15- negative, CD30-negative, CD45-positive germinal center B cells and invariably expresses 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. Almost 80% of patients present with stage I or II lymphadenopathy at diagnosis and have an excellent long-term prognosis.⁶³ In contrast to cHL, the treatment of NLPHL is not clearly defined.

Early-stage NLPHL

Complete surgical excision without adjuvant therapy has exhibited excellent efficacy in paediatric patients with early-stage NLPHL: a Children's Oncology Group study demonstrated a 5-year event-free survival of greater than 75%.^{63,64} Radiation therapy alone is potentially curative in early stage NLPHL. An Australian study showed that 15-year freedom from progression was 82% and OS was 83% among patients who received local radiation.⁶⁵ 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.⁶⁶

Advanced- stage NLPHL

Advanced stage NLPHL Patients who have advanced-stage (III/IV) NLPHL have a worse prognosis than those who have early-stage NLPHL. A multicentre, retrospective analysis in the 1990s 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.

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%.⁶⁷ Multi agent combinations like ABVD and CHOP in combination with rituximab are the most commonly used chemotherapeutic regimens for the treatment of symptomatic patients with advanced NLPHL in the United States.

Conclusions

Treatment for cHL has improved significantly since the ABVD chemotherapeutic combination was invented over 30 years ago. 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 late 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.

References

1. Hodgkin T On some morbid appearances of the absorbent glands and spleen. *Medico-Chirurgical Transactions*. 1832; 17: 68-114.
2. Jaffe ES, Harris NL, Stein H, Vardiman JV, Stein H. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Fourth edition. Lyon, France: IARC Press; 2001.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA: a Cancer Journal for Clinicians*. 2017; 67(1):7-30.
4. Eichenauer DA, Aleman BMP, Andre M, Federico M et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. *Annals of Oncology*. 29 (4): iv19-iv29.
5. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, et al. Bethesda, MD: 2016. Apr, SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. http://seer.cancer.gov/csr/1975_2014/
6. Ambinder RF, Browning PJ, Lorenzana I et al. Epstein-Barr virus and childhood Hodgkin's disease in Honduras and the United States. *Blood*. 1993; 81(2):462-467.

7. Chang KL, Albuja PF, Chen YY, Johnson RM, Weiss LM. High prevalence of Epstein-Barr virus in the Reed-Sternberg cells of Hodgkin's disease occurring in Peru. *Blood*. 1993; 81(2):496-501.
8. Hjalgrim H, Askling J, Rostgaard K, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. *New England Journal of Medicine*. 2003; 349(14):1324-1332.
9. Glaser SL, Clarke CA, Gulley ML, et al. Population-based patterns of human immunodeficiency virus-related Hodgkin lymphoma in the Greater San Francisco Bay Area, 1988-1998. *Cancer*. 2003; 98(2):300-309.
10. Gerard L, Galicier L, Boulanger E, et al. Improved survival in HIV-related Hodgkin's lymphoma since the introduction of highly active antiretroviral therapy. *AIDS*. 2003; 17(1):81-87.
11. Landgren O, Engels EA, Pfeiffer RM, et al. Autoimmunity and susceptibility to Hodgkin lymphoma: a population-based case control study in Scandinavia. *Journal of the National Cancer Institute*. 2006; 98(18):1321-1330.
12. Cobly TV, Hoppe RT, Warnke RA. A clinicopathologic study of 659 cases. *Cancer*. 1981; 49(9):1848-1858.
13. Gulley ML, Eagan PA, Quintanilla-Martinez L, et al. Epstein-Barr virus DNA is abundant and monoclonal in the Reed-Sternberg cells of Hodgkin's disease: association with mixed cellularity subtype and Hispanic American ethnicity. *Blood*. 1994; 83(6):1595-1602.
14. Shimabukuro-Vornhagen A, Haverkamp H, Engert A, et al. Lymphocyte-rich classical Hodgkin's lymphoma: clinical presentation and treatment outcome in 100 patients treated within German Hodgkin's Study Group trials. *Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology*. 2005; 23(24):5739-5745.
15. Diehl V, Sextro M, Franklin J, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. *Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology*. 1999; 17(3):776-783.
16. Mauch PM, Kalish LA, Kadin M, Coleman CN, Osteen R, Hellman S. Patterns of presentation of Hodgkin disease. Implications for etiology and pathogenesis. *Cancer*. 1993; 71(6):2062-2071. Annette Lake, Nixon IJ, Beattie P, Ah-See K et al. P031 (0145) Evaluation of CCL17 (TARC) as a diagnostic biomarker for classical Hodgkin Lymphoma. *HemaSphere*. 2018; 2(53): 14-15.
17. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PETScan in Lymphoma. *Leukaemia & Lymphoma*. 2009; 50(8):1257-1260.
18. El-Galaly TC, d'Amore F, Mylam KJ, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naïve patients with Hodgkin lymphoma. *Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology*. 2012; 30(36):4508-4514.
19. Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *New England Journal of Medicine*. 2010; 363(7):640-652.
20. Cerci JJ, Trindade E, Buccheri V, et al. Consistency of FDG-PET accuracy and cost-effectiveness in initial staging of patients with Hodgkin lymphoma across jurisdictions. *Clinical Lymphoma, Myeloma & Leukaemia*. 2011; 11(4): 314-320.
21. Hutchings M, Loft A, Hansen M, et al. Positron emission tomography with or without computed tomography in the primary staging of Hodgkin's lymphoma. *Haematologica*. 2006; 91(4):482-489.
22. Rigacci L, Vitolo U, Nassi L, et al. Positron emission tomography in the staging of patients with Hodgkin's lymphoma. A prospective multicentric study by the Intergruppo Italiano Linfomi. *Annals of Haematology*. 2007; 86(12):897-903.
23. Kobe C, Dietlein M, Franklin J, et al. Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. *Blood*. 2008; 112(10):3989-3994.
24. Cheson BD, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology*. 2007; 25(5):579-586.
25. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology*. 2007; 25(24):3746-3752.
26. Cerci JJ, Pracchia LF, Linardi CC, et al. 18F-FDG PET after 2 cycles of ABVD predicts event-free survival in early and advanced Hodgkin lymphoma. *Journal of nuclear medicine: official publication, Society of Nuclear Medicine*. 2010; 51(9):1337-1343.
27. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood*. 2006; 107(1):52-59.
28. Jacobs EM, Peters FC, Luce JK, Zippin C, Wood DA. Mechlorethamine HCl and cyclophosphamide in the treatment of Hodgkin's disease and the lymphomas. *Journal of the American Medical Association*. 1968; 203(6): 392-398.
29. Ferme C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early stage Hodgkin's disease. *New England Journal of Medicine*. 2007; 357(19): 1916-1927.
30. Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early stage Hodgkin's lymphoma. *New England Journal of Medicine*. 2010; 363(7):640-652.
31. Nissen NI, Nordentoft AM. Radiotherapy versus combined modality treatment of stage I and II Hodgkin's disease. *Cancer Treatment Reports*. 1982; 66(4):799-803.
32. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2010; 28(27):4199-4206.

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33. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2009; 27(32): 5390-5396.
34. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2013; 31(6):684-689
35. Merli F, Luminari S, Gobbi PG, et al. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPPEBV-CAD in untreated patients with advanced Hodgkin lymphoma: a study by Fondazione Italiana Linfomi. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2016; 34(11):1175-1181
36. Carde P, Karrasch M, Fortpied C, et al. Eight cycles of ABVD versus four cycles of BEACOPPescalated plus four cycles of BEACOPPbaseline in stage III to IV, international prognostic score ≥ 3 , high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 Intergroup Trial. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2016; 34(17):2028-2036
37. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *New England Journal of Medicine*. 2011; 365(3):203-212
38. Skoetz N, Will A, Monsef I, Brillant C, Engert A, von Tresckow B. Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma [serial online]. *The Cochrane database of systematic reviews*. 2017;5:CD007941.
39. Sieniawski M, Reineke T, Nogova L, et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG). *Blood*. 2008; 111(1):71-76.
40. Jurczak W, Krochmalczyk D, Pabian W et al. Quality of life and fertility in Hodgkin disease patients treated with escalated BEACOPP. 2009; 94:35.
41. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PETCT scan in advanced Hodgkin's lymphoma. *New England Journal of Medicine*. 2016; 374(25):2419-2429.
42. Lohri A, Barnett M, Fairey RN, et al. Outcome of treatment of first relapse of Hodgkin's disease after primary chemotherapy: identification of risk factors from the British Columbia experience 1970 to 1988. *Blood*. 1991; 77(10):2292-2298.
43. Majhail NS, Weisdorf DJ, Defor TE, et al. Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. *Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation*. 2006; 12(10):1065-1072.
44. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993; 341:1051-1054.
45. 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(9323):2065-2071.
46. Rancea M, Monsef I, von Tresckow B, Engert A, Skoetz N. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. *Cochrane Database Systematic Reviews*. 2013;6:CD009411.
47. Chen R, Gopal AK, Smith SE, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2016; 128(12):1562-1566.
48. Steidl C, Connors JM, Gascoyne RD. Molecular pathogenesis of Hodgkin's lymphoma: increasing evidence of the importance of the microenvironment. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2011; 29(14):1812-1826.
49. Yamamoto R, Nishikori M, Kitawaki T et al. PD-1-PD-1 ligand interaction contributes to immunosuppressive microenvironment of Hodgkin lymphoma. *Blood*. 2008; 111(6):3220-3224.
50. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *New England Journal of Medicine*. 2015 ;372(4):311-319.
51. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *The Lancet Oncology*. 2016; 17(9):1283-1294.
52. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2017; 35(19):2125-2132.
53. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Annals of oncology: Official journal of the European Society for Medical Oncology*. 2015; 26(12):2375-2391.
54. 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(9323):2065-2071.
55. Viviani S, Di Nicola M, Bonfante V, et al. Long-term results of high-dose chemotherapy with autologous bone marrow or peripheral stem cell transplant as first salvage treatment for relapsed or refractory Hodgkin lymphoma: a single institution experience. *Leukaemia & lymphoma*. 2010;51(7):1251-1259.
56. Moskowitz CH, Yahalom J, Zelenetz AD, et al. High-dose chemo-radiotherapy for relapsed or refractory Hodgkin lymphoma and the significance of pre-transplant functional imaging. *British Journal of Haematology*. 2010; 148(6):890-897.
57. Lavoie JC, Connors JM, Phillips GL, et al. High-dose chemotherapy and autologous stem cell transplantation for primary refractory or relapsed Hodgkin lymphoma: long-term outcome in the first 100 patients treated in Vancouver. *Blood*. 2005; 106(4):1473

58. Peggs KS, Hunter A, Chopra R, et al. Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantation. *Lancet*. 2005; 365(9475): 1934-1941.
59. Peggs KS, Sureda A, Qian W et al. Reduced-intensity conditioning for allogeneic haematopoietic stem cell transplantation in relapsed and refractory Hodgkin lymphoma: impact of alemtuzumab and donor lymphocyte infusions on long-term outcomes. *British Journal of Haematology*. 2007; 139(1):70-80.
60. Sureda A, Robinson S, Canals C, et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *Journal of Clinical oncology: official journal of the American Society of Clinical Oncology*. 2008 ;26(3):455-462.
61. Sarina B, Castagna L, Farina L et al. Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. *Blood*. 2010; 115(18):3671-3677.
62. Mauz-Korholz C, Gorde-Grosjean S, Hasenclever D, et al. Resection alone in 58 children with limited stage, lymphocyte-predominant Hodgkin lymphoma—experience from the European network group on paediatric Hodgkin lymphoma. *Cancer*. 2007; 110(1):179-185.
63. Appel BE, Chen L, Buxton AB, et al. Minimal treatment of low-risk, pediatric lymphocyte-predominant Hodgkin lymphoma: a report from the Children's Oncology Group. *Journal of Clinical oncology: official journal of the American Society of Clinical Oncology*. 2016; 34(20):2372-2379.
64. Wirth A, Yuen K, Barton M, et al. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. *Cancer*. 2005; 104(6):1221-1229.
65. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG). *International Journal of radiation oncology, biology, physics*. 2014; 89(4):854-862.
66. Advani RH, Horning SJ, Hoppe RT, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. *Journal of Clinical oncology: official journal of the American Society of Clinical Oncology*. 2014; 32(9):912-918.