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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

Hodgkin lymphoma: A 2020 update on diagnosis, risk-stratification, and management

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Abstract

Disease overview: Hodgkin lymphoma (HL) is an uncommon B-cell lymphoid malignancy affecting 8480 new patients annually and representing approximately 10% of all lymphomas in the United States.

Diagnosis: Hodgkin lymphoma is composed of two distinct disease entities: classical HL and nodular lymphocyte predominant HL. Nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL are subgroups of classical HL.

Risk stratification: An accurate assessment of the stage of disease in patients with HL is critical for the selection of the appropriate therapy. Prognostic models that identify patients at low or high risk for recurrence, as well as the response to therapy as determined by positron emission tomography (PET) scan, are used to optimize therapy.

Risk-adapted therapy: Initial therapy for HL patients is based on the histology of the disease, the anatomical stage and the presence of poor prognostic features. Patients with early stage disease are typically treated with combined modality strategies utilizing abbreviated courses of combination chemotherapy, followed by involved-field radiation therapy. Patients with advanced stage disease receive a longer course of chemotherapy, often without radiation therapy. However, newer agents including brentuximab vedotin and anti-PD-1 antibodies are now being incorporated into frontline therapy.

Management of relapsed/refractory disease: High-dose chemotherapy (HDCT) followed by an autologous stem cell transplant (ASCT) is the standard of care for most patients who relapse following initial therapy. For patients who fail HDCT with ASCT, brentuximab vedotin, PD-1 blockade, non-myeloablative allogeneic transplant or participation in a clinical trial should be considered.

1 | DISEASE OVERVIEW

Hodgkin lymphoma (HL) affects approximately 8480 new patients In the United States each year.[1] The disease has a bimodal distribution with an increased incidence in young adults as well as in patients 55 years and older.[2] There are no clearly defined risk factors for the development of this disease and the cause of HL remains unknown. Factors shown to be associated with HL include familial factors, viral exposures and immune suppression.[2] Same sex siblings of patients with HL have a 10-fold higher risk for developing the disease.[3,4] And, a monozygotic twin of a patient with HL has a significantly increased risk of developing HL, when compared to a dizygotic twin sibling of a patient with HL.[5,6] While these familial factors may suggest a genetic cause for this disease, research also suggests that an abnormal immune response to infection may play a role in the pathogenesis of HL. Epidemiologic and serologic studies have implicated Epstein-Barr

virus (EBV) in the etiology of HL and the EBV genome was detected in tumor specimens from patients with HL.[7] Other childhood infectious illnesses including chickenpox, measles, mumps, rubella, and pertussis, however, are negatively associated with the risk of HL and are possibly protective.[8] There is also an association with human immunodeficiency (HIV) infection, in that HIV infected patients have a significantly increased risk of HL when compared to the general population.[9] Overall, HL in immunosuppressed patients, including those who are HIV positive, is associated with advanced stage of disease at presentation, unusual sites of disease, and a poorer outcome after initial therapy.[10,11]

Over the last four decades, advances in radiation therapy and the addition of combination chemotherapy have significantly increased the cure rate of patients with HL. Currently, more than 80% of all newly diagnosed patients younger than 60 years are likely to be cured of their disease.

2 | DIAGNOSIS

At the time of diagnosis, the majority of patients with HL present with supradiaphragmatic lymphadenopathy. Patients commonly present with cervical, anterior mediastinal, supraclavicular, and axillary lymph node involvement, while the inguinal areas are less frequently involved. Approximately one-third of patients present with systemic symptoms that include fever, night sweats, and weight loss, and many patients also present with chronic pruritus. While the disease most commonly involves contiguous lymph node groups, Hodgkin lymphoma may also affect extranodal tissues by direct invasion or by hematogenous spread. The most commonly involved extranodal sites are the spleen, lungs, liver, and bone marrow.

The initial diagnosis of HL can only be made by a biopsy. Fine needle aspiration or core needle biopsies are inadequate because the architecture of the lymph node is extremely important for an accurate diagnosis. Hodgkin lymphoma is a unique malignancy in that the tumor cells constitute the minority of the cellular population, and an inadequate biopsy may fail to include malignant cells in the specimen.[12] To confirm the diagnosis, it is necessary to identify the malignant Reed-Sternberg cell, which is of follicular center B cell origin,[13,14] within the appropriate cellular environment of normal reactive lymphocytes, eosinophils and histiocytes.

Hodgkin lymphoma is composed of two distinct disease entities; the more commonly diagnosed classical HL and the rare nodular lymphocyte predominant HL.[15] Nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL are subgroups under the designation of classical HL.

2.1 | Classical Hodgkin lymphoma

The presence of malignant multinucleated giant Reed-Sternberg cells within the characteristic reactive cellular background is the pathologic hallmark of classical HL. Painless lymphadenopathy is the most common clinical manifestation of classical HL, although each histological subtype has its own unique clinical features.[16] Nodular sclerosis, the most common subtype, tends to effect adolescent and young adults more commonly and usually presents with localized disease involving cervical, supracavicular and mediastinal regions. Mixed cellularity HL is more prevalent in the pediatric as well as older age groups, and is commonly associated with a more advanced stage of disease and a poorer prognosis. The incidence of lymphocyte depletion HL appears much lower than previously reported, with many of these cases reclassified as non-Hodgkin lymphoma. This subtype occurs mainly in older age patients and in patients with acquired immune deficiency syndrome. These patients typically present with symptomatic extensive disease without peripheral lymphadenopathy. Lymphocyte rich classical HL represents a subtype similar to nodular lymphocyte predominant HL (see below) on morphologic grounds; however the Reed-Sternberg cells have a more classical immunophenotype consistent with classical HL.

Recent research has found overexpression of programmed death-1 (PD-1) ligands, including PD-L1 (CD274/B7-H1) and PD-L2 (CD273/B7-DC), on Reed-Sternberg cells.[17-19] Copy number variation and genetic alterations at chromosome 9p24.1, as well as increased JAK2 signaling, account for the majority of cases with overexpression of PD-L1 and PD-L2.[17] The PD-L1/PD-L2 alterations are a defining feature of Hodgkin lymphoma and result in very high expression of PD-L1 or PD-L2 on the cell surface, thereby protecting Reed-Sternberg cells from T-cell mediated killing. While amplification of 9p24.1 is more common in patients with advanced stage disease and is associated with shorter progression free survival in patients treated with chemotherapy, PD-L1 expression and MHC class II positivity on Reed-Sternberg cells are predictors of a favorable outcome after PD-1 blockade.[18,19]

2.2 | Nodular lymphocyte predominant Hodgkin lymphoma

Nodular lymphocyte predominant HL constitutes a unique clinical pathologic entity that is significantly different to classical HL. Pathologically, lymphocyte predominant HL lacks the typical Reed-Sternberg cells, and instead is characterized by a neoplastic population of larger cells with folded lobulated nuclei known as lymphocytic and histiocytic (L&H) cells. Unlike classical HL, these cells are CD20+ and commonly negative for CD30.[20] Lymphocyte predominant HL is more frequently seen in men and constitutional symptoms at presentation as well as extranodal disease are rare. Patients usually present with limited nodal disease that classically affects the neck region and spares the mediastinum. The natural history of lymphocyte predominant HL differs from classical HL in that it has an indolent course with a tendency for late recurrences.[21]

3 | RISK STRATIFICATION

An accurate assessment of the stage of disease in patients with HL is critical for the selection of the appropriate therapy. The staging

system for patients with HL is based on whether the involved lymph nodes are on one or both sides of the diaphragm, the number of involved sites, whether the sites of involvement are bulky, whether there is contiguous extranodal involvement or disseminated extranodal disease, and whether typical systemic symptoms (B symptoms) are present. Fluorodeoxyglucose positive emission tomography (FDG-PET) scanning has emerged as an important tool in the staging of patients with HL, in that it significantly adds to the staging information obtained using other standard radiographic methods.[22]

Many patients with HL can be cured with standard treatment and are therefore at risk for potential long-term complications. Factors that identify patients at low or high risk for recurrence would therefore be most useful in optimizing therapy, based on the patient's expected clinical outcome, to avoid over-treatment of some patients and under-treatment of others. Prognostic factors for early stage HL have been identified and include the presence of a large mediastinal mass, an elevated sedimentation rate, involvement of multiple nodal sites, extranodal involvement, age ≥ 50 years, or massive splenic disease.[23] In contrast, in patients with advanced HL, disease bulk and other traditional prognostic variables have been found to be less predictive of outcome. A different prognostic scoring system was therefore developed for these patients by the International Prognostic Factor Project on advanced HL.[24] This study identified seven variables (age ≥ 45 years, presence of stage IV disease, male sex, white blood count ≥15 000 cells/μL, lymphocyte count <600 cells/μL, albumin <4.0 g/dL, hemoglobin <10.5 g/dL) that predicted patient outcome in a multivariate analysis. Patients with five or more factors were found to have a 5-year freedom from progression of 42%, while patients with no negative prognostic factors had an 84% likelihood of being free from progression at 5 years.

4 | RISK-ADAPTED INITIAL THERAPY

The predominant factors that determine the initial choice of therapy for HL patients are the histology of the disease (classical HL or nodular lymphocyte predominant HL), the anatomical stage of disease (limited or advanced disease), the presence of poor prognostic features, the presence of constitutional symptoms and the presence of bulky disease, defined as a single site of disease >10 cm in diameter. During the course of treatment, FDG-PET scanning now plays a role in decisions to complete therapy as planned, or to add or omit components of treatment. A positive interim FDG-PET scan after two cycles of treatment may result in intensification of therapy. And, a positive PET scan at the end of treatment may result in the addition of consolidation radiotherapy to the positive sites. A positive PET scan at any point may also result in a repeat biopsy to confirm or exclude persistent disease. The use of PET scans in this fashion is based on studies showing that patients with a positive FDG-PET scan at the completion of treatment, have a significantly higher recurrence rate regardless of the findings on CT scan.[25,26] Also, a FDG-PET done early in the course of treatment (after two cycles) predicted progression-free survival (PFS) and overall survival (OS) for patients with HL, and was a better predictor of outcome than stage, extranodal disease or other prognostic factors.[27,28]

4.1 | Initial therapy

The current standard of care for institutions that treat patients with HL is to have different treatment strategies for HL patients with early stage disease with favorable prognostic features, those with early stage disease but who have poor prognostic features, or those with advanced disease. As a general rule, patients with early stage disease are treated with combined modality strategies utilizing abbreviated courses of combination chemotherapy, followed by involved-field radiation therapy (IFRT) in most cases, while those with advanced stage disease receive a longer course of chemotherapy without radiation therapy. Newer agents, including brentuximab vedotin and anti-PD-1 antibodies, are now being included in standard combination therapy.

4.1.1 | Early stage favorable HL

Treatment strategies for early stage HL (stages I-IIA) have changed significantly in the last few decades. Initially, extended field radiation was considered the standard therapy. However, due to the recognition of high relapse rates with significant long-term complications, extended field radiation therapy to involve adjacent lymph node areas is no longer used.[29] A randomized comparison of patients treated with subtotal nodal radiation therapy, with or without ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine), and those who received ABVD alone, found that patients who received subtotal nodal radiation therapy had a poorer overall survival, and a higher rate of death from causes other than Hodgkin lymphoma.[30] Therefore, for favorable early stage disease, short duration chemotherapy for control of occult lesions, combined with IFRT restricted only to involved lymph node areas is currently standard practice. Most groups will give 2-4 cycles of combination chemotherapy followed by IFRT to a dose of approximately 20-35 Gy.[31] This approach is based on data from a four arm study of 1370 patients performed by the GHSG. The study randomized early stage HL patients with favorable prognostic factors, to either two or four cycles of ABVD chemotherapy, and 20 or 30 Gy IFRT. There was no difference between the four groups as regards response to therapy, PFS and OS. Note, ABVD for two cycles, followed by 20 Gy IFRT is therefore currently the standard treatment for early stage favorable prognosis (no adverse risk features) Hodgkin lymphoma.[32]

4.1.2 | Early stage unfavorable HL

It is generally accepted that patients with stage I and II disease who present with adverse risk factors, should be treated with

chemotherapy in combination with radiation therapy. However, the optimal number of chemotherapy cycles, as well as the optimal chemotherapy regimen, and the dose of radiation as well as the field sizes, are the subject of ongoing studies and debate. This group of patients usually consists of those with bulky mediastinal masses or those with extranodal disease. In these patients, the use of four cycles of combination chemotherapy with IFRT is generally accepted as the treatment of choice.[33,34] A clinical trial was done of 1395 patients with stage I/IIA HL disease, with unfavorable features including large mediastinal masses, extranodal disease, high erythrocyte sedimentation rate (ESR) or ≥3 nodal sites. Patients were randomized to ABVD for four cycles or baseline doses of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) for four cycles, plus either 20 or 30 Gy IFRT. Freedom from treatment failure was worse if 20 Gy rather than 30 Gy was used with ABVD, however, similar outcomes were seen between 20 and 30 Gy when used with BEACOPP. The conclusion was that ABVD for four cycles plus 30 Gy IFRT is the standard for these patients.[34] A subsequent study looked at intensifying the chemotherapy used in this patient group. In this trial, 1528 qualified patients with early stage unfavorable HL received ABVD for four cycles, or escalated doses of BEACOPP for two cycles plus ABVD for two cycles. All patients got 30 Gy IFRT. The freedom from treatment failure favored the aggressive chemotherapy arm—with a difference of 7.2% at 5 years—but there was no difference in overall survival, and increased toxicity was seen in the aggressive chemotherapy arm.[35] There were no differences in treatment-related mortality or secondary malignancies. Subsequent studies have therefore been developed to determine whether including novel agents, such as brentuximab vedotin and PD-1 blocking antibodies, can maintain efficacy and decrease potential toxicities in these patients.[36,37] Results from these trials so far have shown that these strategies are safe, but randomized trials will be needed to confirm that these combinations are as effective and potentially less toxic than standard approaches.

4.1.3 | Response-adapted treatment

To determine the optimal amount of treatment needed, multiple studies have used functional imaging to provide an early indication of chemosensitivity in HL. Note, FDG-PET has predominantly been used as an interim read-out of efficacy, and its utility has been enhanced by the development of a highly reproducible five-point scale for reporting results.[38] This approach allows for the detection of residual active lymphoma when compared to conventional computed tomography.[28] Results from two large studies illustrate the use of a PET-directed approach. The United Kingdom National Cancer Research Institute RAPID study randomized patients with non-bulky early stage disease who had a negative interim PET (score of 1 or 2) after three cycles of ABVD, to either 30 Gy IFRT or no further therapy, and found that the 3-year PFS and overall survival were not significantly different between the two arms.[39] However, there was a trend toward inferior disease control in patients who did not receive radiotherapy, and the difference became statistically significant when patients who did not receive treatment as per protocol were excluded (97.1% vs 90.8%).

Similarly, the EORTC/ LYSA/FIL H10 study compared standard treatment with ABVD and involved-node radiotherapy (INRT), to a non-radiotherapy approach using further chemotherapy, for patients with negative FDG-PET scans after two cycles of ABVD. An escalation strategy was adopted if patients were PET-positive.[40] In this study, PET-positive patients were switched to two cycles of escalated BEACOPP and INRT, while PET-negative patients received either ABVD followed by INRT (control arm) or ABVD only (experimental arm). The authors found that the PET response after two cycles of ABVD allowed for early treatment adaptation. In the PET-positive patient cohort, the 5-year PFS improved from 77.4% for standard ABVD + INRT to 90.6% for intensification to escalated BEACOPP + INRT (P = .002). In PET-negative patients, however, the 5-year PFS rates in the patients with favorable disease were 99.0%, vs 87.1% in favor of ABVD + INRT, and in the unfavorable group, 92.1% vs 89.6% in favor of ABVD + INRT. For patients with both favorable and unfavorable prognostic factors, non-inferiority of ABVD only compared with combined modality treatment could not be demonstrated.

The evidence therefore suggests that the use of combined modality treatment produces excellent disease control in patients with early stage HL, and that a high percentage of patients are cured with initial therapy. There is however a large proportion of patients, approximately 90%, who will be cured with chemotherapy alone. The number needed to treat with radiation in order to achieve one extra cure is therefore between 15 and 30 based on these studies. Given these excellent results and the potential late toxicity from radiotherapy, many patients may prefer the slightly higher risk of recurrent Hodgkin lymphoma if radiotherapy is omitted, to the potential for long-term complications if radiotherapy is given. In general, however, the outcomes with both approaches are excellent, and the small reduction in disease control does not appear to have any detrimental effect upon overall survival in either study.

4.1.4 | Advanced disease

In patients with advanced disease (stages IIB-IV), the challenge is to increase the number of patients with durable remissions while decreasing the likelihood of long-term side effects. Initially, the MOPP regimen (nitrogen mustard, vincristine, procarbazine, prednisone) was developed for patients who progressed after radiation therapy, and the long-term results with the MOPP regimen showed this to be an effective therapy. This combination resulted in a freedom from progression rate of 54% and an overall survival of 48% at 20 years.[41] Although the MOPP regimen significantly changed the outcome of patients who previously would have died of progressive disease, approximately one-third of patients subsequently relapsed. Since then, multiple other regimens have been developed in an attempt to improve on the efficacy of this regimen.

The ABVD chemotherapy regimen was then developed and also showed significant clinical activity with potentially less toxicity.

This led to a randomized trial comparing alternating cycles of MOPP and ABVD chemotherapy to MOPP chemotherapy alone. The alternating regimen was found to be superior as regards the complete remission rate, freedom from progression, and overall survival.[42] Several major randomized studies over the last 20 years have attempted to identify the regimen with the greatest activity and the most favorable side effect profile. Initially MOPP, ABVD, and MOPP alternating with ABVD were compared.[43] In this study, the complete response rate and freedom from progression was worse for patients receiving MOPP chemotherapy alone, compared to those receiving ABVD or the alternating regimen. Two further studies compared the MOPP/ABVD hybrid regimen to MOPP alternating with ABVD, and the regimens were found to be equivalent.[44] When the MOPP/ABV hybrid regimen was compared to ABVD, the ABVD arm showed superiority with less toxicity.[45] The results of all of these trials led to ABVD chemotherapy being regarded as the treatment of choice for patients with advanced HL based on its efficacy, relative ease of administration, and acceptable side effect profile.

To further minimize toxicity, the Stanford V regimen was developed which incorporated the active agents from MOPP and ABVD into a brief dose intense regimen and combined this 12 week regimen with radiation therapy.[46] The results initially obtained showed a 5-year freedom from progression in 142 patients of 89% and an overall survival of 96%. Similar results were obtained in a multi-institutional ECOG study.[47] This regimen was tested against ABVD in a number of randomized trials. Initial studies suggested that ABVD might be superior to the Stanford V regimen. With long term follow up; the 10-year failure-free survival was 75%, and 49% for the ABVD and Stanford V regimens respectively. The differences in outcome however may be explained by the fact that the administration of radiotherapy in the Stanford V arm differed from what was originally described.[48] Two subsequent randomized trials comparing ABVD to Stanford V have found similar response rates, failure-free and overall survival.[49,50] The frequency of adverse events were similar between the two regimens with patients receiving ABVD experiencing more pulmonary toxicity, and patients receiving Stanford V having a greater number of other toxicities.

The GHSG also developed new regimens for patients with advanced HL including standard and dose escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).[51] A large randomized trial comparing COPP (cyclophosphamide, vincristine, procarbazine, prednisone) alternating with ABVD to either dose escalated BEACOPP or standard BEACOPP showed better tumor control and overall survival for patients receiving dose escalated BEACOPP.[23] The results were updated at 10 years and continued to show improved outcomes for patients treated with escalated BEACOPP.[52] While these results are encouraging, but it is important to note that acute myeloid leukemia or myelodysplastic syndrome were more frequently seen in patients treated with escalated BEACOPP. A further study compared six cycles of ABVD to four cycles of escalated BEACOPP, followed by two cycles of standard BEACOPP. This study also had a third arm in which patients received six cycles of a multi-drug intensive regimen. When the results from the ABVD arm were compared the BEACOPP arm, there was an improved PFS with BEACOPP, but the OS in both arms was similar. More toxicity was seen in BEACOPP treated patients, but there was a benefit for BEACOPP in poor risk patients.[53] Further randomized studies have been done to determine the optimal number of cycles of BEACOPP needed to maintain the improved outcome and also decrease toxicity. The GHSG found that six cycles of escalated BEACOPP, followed by radiotherapy administered only to PET positive masses measuring more than 2.5 cm, was more effective in terms of freedom from treatment failure and less toxic than eight cycles of the same regimen.[54]

Subsequently, a randomized comparison of ABVD and BEACOPP in advanced stage Hodgkin lymphoma was reported.[55] Three hundred and thirty-one patients with poor risk Hodgkin lymphoma were enrolled, and local radiotherapy was added to therapy as indicated. Patients with residual or progressive disease were subsequently treated with salvage therapy including stem cell transplantation. The authors analyzed the outcome after initial therapy and also after salvage therapy. The freedom from first progression favored patients receiving BEACOPP and was 85% in that group compared to 73% among patients treated with ABVD (P = .004). However, after completion of all planned therapy including salvage therapy for those with residual or progressive disease, the 7-year rate of freedom from second progression was 88% in the BEACOPP group, and 82% in the ABVD group (P = .12). And, the 7-year overall survival rate was 89% and 84%, respectively (P = .39). Severe adverse events were more frequent in the BEACOPP patients than in the ABVD patients. These results have led some to suggest that initial therapy may not need to be highly aggressive in all patients as those who relapse may be salvaged with subsequent intensive therapy.[56] Others have pointed out that overall survival was a secondary endpoint in this study, and that the study was small compared to other similar trials.[57] Furthermore, a network meta-analysis of all comparative trials showed a survival benefit with escalated BEACOPP when compared to ABVD.[58] Additional follow up will be needed to confirm whether patient outcomes are similar regardless of the approach.

Recent trials have utilized PET scans to identify patients who may benefit from intensification (or de-escalation) of therapy and the RATHL study is illustrative of this approach.[59] In this study, 1214 patients with advanced Hodgkin lymphoma received two cycles of ABVD chemotherapy followed by an interim PET scan. Patients with a negative scan (1-3 on the 5-point scale) were randomized to ABVD or AVD (without bleomycin) for four more cycles. Patients with a positive PET scan (4, 5) proceeded to intensification of therapy with either four cycles of BEACOPP-14 or three cycles of escalated BEACOPP, followed by a repeat PET scan. If this scan was negative, patients completed therapy with two further cycles of BEACOPP-14, or one cycle of escalated BEACOPP. Patients with a persistently positive PET scan came off study and received salvage therapy. In patients with a negative interim PET scan, the 3-year progression-free survival rate and overall survival rate in the ABVD group were 85.7% and 97.2% respectively, while the corresponding rates in the AVD group were 84.4% and 97.6%. Notably, respiratory adverse events were more

severe in the ABVD group than in the AVD group. The conclusion from this arm of the study was that the omission of bleomycin from the ABVD regimen, after a negative interim PET scan, resulted in a lower incidence of pulmonary toxicity than seen with continued ABVD, but not significantly lower efficacy. In 174 patients with a positive interim PET scan, intensification of therapy to BEACOPP resulted in 74.4% of patients having negative findings on an end of therapy PET scan. In this group, the 3-year progression-free survival rate was 67.5% and the overall survival rate 87.8%, suggesting that an intensification approach may improve results and supporting response-adapted therapy in advanced Hodgkin lymphoma.

To potentially further improve the outcome of advanced HL patients with poor prognostic features, the role of high dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) has been evaluated as part of initial therapy for these patients. Patients with advanced unfavorable HL achieving a complete or partial remission after four courses of doxorubicin-containing regimens were found to have a favorable outcome with conventional chemotherapy, and no benefit from an early intensification with HDCT and ASCT was shown.[60]

The strategies discussed above have largely focused on intensification of therapy to improve the outcome of patients with advanced stage Hodgkin lymphoma. A more recent approach has been to add novel agents to standard chemotherapy regimens. Novel agents currently being used in combination with chemotherapy in the frontline setting include brentuximab vedotin and PD-1 blocking antibodies. Brentuximab vedotin was initially combined with ABVD, and subsequently substituted for bleomycin, in a phase I study.[61] In this combination study, complete responses after the conclusion of front-line therapy were achieved in 95% of the 22 patients receiving ABVD plus brentuximab, and in 96% of the 25 receiving AVD plus brentuximab. However, significant pulmonary toxicity was seen when brentuximab vedotin was administered in combination with bleomycin, resulting in the concurrent use of bleomycin and brentuximab vedotin being contraindicated. Based on the very high response rate, and the fact that brentuximab vedotin was well tolerated when given with AVD chemotherapy, a randomized phase III trial comparing ABVD and AVD, plus brentuximab vedotin has been completed.[62] The primary endpoint was an improvement in the modified progression-free survival (defined as time to progression, death, or evidence of incomplete response followed by subsequent anticancer therapy) and this endpoint was met (P = .035). The 2-year modified progression-free survival was 82.1% with AVD plus brentuximab vedotin compared to 77.2% with ABVD. Secondary endpoints including complete response (CR) rate, overall response rate and event-free survival also trended in favor of AVD plus brentuximab vedotin. Neutropenia, infections and peripheral neuropathy were more common in the brentuximab vedotin plus AVD arm, while pulmonary toxicity was more frequent with ABVD. The investigators concluded that brentuximab vedotin plus AVD is a new frontline option for patients with advanced-stage Hodgkin lymphoma.

The GHSG also explored the use of brentuximab in combination with BEACOPP and developed two new regimens, namely a more conservative variant BrECAPP (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, procarbazine, prednisone), and a more aggressive variant BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone). The results of a randomized phase II trial suggest that use of these combinations, which incorporate an anti-CD30 targeted approach, is feasible without compromising the efficacy associated with escalated BEACOPP.[63]

Recent clinical trials have also added anti-PD1 antibodies to AVD chemotherapy (bleomycin omitted) in the frontline setting for patients with newly diagnosed, untreated HL. These studies have first used the PD-1 antibodies alone for 2-3 cycles, followed by the subsequent administration or addition of chemotherapy.[64,65] Both studies demonstrated high complete response rates and the progression free survival suggested promising activity of the combination of immune checkpoint blockade and chemotherapy. The combination was well tolerated and the results have led to a national randomized trial in the United States comparing brentuximab vedotin plus AVD chemotherapy to nivolumab, plus AVD chemotherapy for newly diagnosed patients with advanced stage HL (ClinicalTrials.gov Identifier: NCT03907488).

Elderly patients constitute a uniquely challenging cHL population, as they typically do not tolerate more intense regimens very well. Brentuximab vedotin and PD-1 blocking antibodies are now being used in elderly, either individually in combination with more tolerable chemotherapy regimens or together without the addition of chemotherapy. In a study of 48 patients 60 years or older, patients with advanced stage cHL first received two cycles of brentuximab vedotin alone, then six cycles of AVD chemotherapy, followed by four cycles of brentuximab vedotin.[66] The overall response and complete remission rates after initial brentuximab vedotin lead-in doses were 82% and 36%, respectively, and 95% and 90%, respectively, after six cycles of AVD among 42 evaluable patients. The regimen was well tolerated and the 2-year event-free survival, progression-free survival, and overall survival rates were 80%, 84%, and 93%, respectively, which is excellent for a cohort of elderly patients.

Brentuximab vedotin has also been combined with nivolumab, without any chemotherapy, in elderly patients.[67] Patients received brentuximab vedotin 1.8 mg/kg plus nivolumab 3 mg/kg on a 3-week cycle for ≤16 cycles. Based on the 18 of 21 evaluable subjects, the overall response rate was 100%, with a 72% complete response rate and a 28% partial response rate. These promising results suggest that incorporating novel agents into frontline therapy may be particularly beneficial for elderly patients.

In summary, ABVD chemotherapy remains the most widely used treatment in the United States for patients with advanced stage HL. However, dose intense regimens such as escalated BEACOPP could be considered in patients with advanced disease and multiple poor prognostic factors. Based on recent data, the addition of novel agents to established combinations is resulting in improved outcomes for HL patients. Brentuximab vedotin plus AVD chemotherapy is now also a standard approach for patients with stage III/IV disease, and the addition of nivolumab to AVD in the same population appears very promising. To determine the optimal use of these agents,

randomized trials are now testing the addition of PD-1 blocking antibodies to chemotherapy compared to brentuximab vedotin added to chemotherapy.

4.1.5 | Nodular lymphocyte predominant Hodgkin lymphoma

An exception to the management approach outlined above are early stage patients with nodular lymphocyte predominant HL. Patients with favorable stage IA disease, with no significant risk factors, can commonly be managed with lymph node excision followed by a "watch and wait" approach, or with IFRT to a dose of approximately 20-30 Gy. More advanced stage patients with nodular lymphocyte predominant HL are commonly treated with ABVD, often in combination with rituximab, because the malignant cells express CD20. Clinical trials are in progress to define the optimal therapy for this disease.

4.2 | Management of relapsed/refractory disease

Despite the high cure rate with initial therapy, approximately 5% to 10% of HL patients are refractory to initial treatment, and 10% to 30% of patients will relapse after achieving an initial complete remission.[47,68] So, HDCT followed by an ASCT is the standard of care for many patients who relapse following a response to initial chemotherapy.

4.2.1 | Primary refractory disease

Patients with primary refractory disease, defined as progression or non-response during induction treatment or within 90 days of completing treatment, generally have a dismal clinical course. Second-line chemotherapy for these patients produces low response rates, with long-term disease-free survival in only 5% to 10% of patients.[69,70] Therefore, in these patients, high dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is currently considered to be the treatment of choice. A number of retrospective analyses have suggested that patients treated with ASCT have a superior long term outcome when compared to patients treated with chemotherapy.[71,72] An analysis of treatment outcome in primary progressive patients showed that the 5-year freedom from failure and overall survival for all patients were 17% and 26% respectively, compared to 31% and 43% for those treated with HDCT and an ASCT.[73] Other studies have further confirmed that patients receiving HDCT followed by ASCT have a better outcome than patients treated with chemotherapy.[73-75] However, a majority of these patients still relapse following HDCT and ASCT.

4.2.2 | Relapsed disease

Between 10% and 30% of patients will relapse following an initial chemotherapy regimen. Patients with progressive disease have typically been treated with salvage chemotherapy regimens similar to what has been used in patients with non-Hodgkin lymphoma. Most eligible patients have then proceeded to undergo an ASCT. However, no randomized trials have been done comparing the effectiveness of different conventional salvage chemotherapeutic regimens, and no optimal salvage regimen has been identified. While treatments with most salvage regimens result in high overall response rates, the goal of salvage therapy is to increase the number of patients achieving a complete response. Recent studies have therefore evaluated whether the addition of brentuximab vedotin or anti-PD-1 antibodies to salvage chemotherapy may improve the complete response rates, and increase the number of patients who subsequently receive an ASCT. The combinations of bendamustine plus brentuximab vedotin, brentuximab vedotin plus nivolumab, and brentuximab vedotin plus ICE (ifosfamide, carboplatin, etoposide) have resulted in complete response rates of 74%, 61% and 76% respectively.[76-78] Despite the responses to salvage therapy, this treatment alone is insufficient and patients commonly relapse and subsequently die of disease progression. A consolidation approach that typically includes HDCT and an ASCT is needed for patients to have durable benefit.

Initial phase II studies suggested that HDCT followed by ASCT may produce a better long-term disease-free survival than expected with conventional chemotherapy in 30% to 65% of patients.[79,80] Two subsequent randomized studies confirmed an improved outcome in patients with relapsed HL treated with HDCT, followed by ASCT as compared with conventional salvage chemotherapeutic regimens.[81,82] In both studies the event-free survival after 3 years of patients treated with HDCT was over 50%.

Not all patients are eligible for, or may benefit from, an ASCT. Elderly patients treated with an ASCT have increased treatment-related mortality, and commonly have an inferior event free survival when compared to younger patients.[83] Some patients have relentlessly progressive disease and have been treated with tandem autologous stem-cell transplantation[84] or allogeneic transplantation.[85] Preliminary results have suggested that these therapies are feasible, but toxicity and relapses have been common.

To potentially prevent or delay progression post-transplant, particularly in patients with unfavorable risk factors, a randomized, double blind, placebo-controlled phase 3 trial of brentuximab vedotin was reported.[86] In this study, 329 patients were randomized to 16 doses of brentuximab vedotin or placebo starting 30-45 days post autologous stem cell transplant. Patients were included if they had unfavorable risk factors defined as primary refractory disease, progression within 12 months of an initial response to frontline therapy, or extranodal involvement prior to salvage therapy. The median PFS was 42.9 months for the brentuximab vedotin treated patients compared to 24.1 months in the placebo arm. This confirmed a benefit for brentuximab vedotin therapy post-transplant in high-risk patients. A much smaller study of 30 patients evaluated the use of pembrolizumab given for eight doses post-transplant in a similar cohort of patients.[87] The primary endpoint was that pembrolizumab would improve the progression-free survival at 18 months after ASCT, from 60% to 80%. The progression-free survival at 18 months for the

28 evaluable patients was 82%, meeting the primary end point. However, the benefit of immune checkpoint blockade post-ASCT will need to be confirmed in a randomized trial.

4.2.3 | Therapeutic options following relapse after HDCT and ASCT

Patients with progression of disease after ASCT uniformly have a poor outcome. In a study of HL patients who failed ASCT, the median time to progression after the next chemotherapy was only 3.8 months, and the median survival after ASCT failure was 26 months.[88] For patients who fail HDCT with ASCT, few good chemotherapy options exist. Among cytotoxic drugs, only vinorelbine[89] and gemcitabine[90] have shown promising activity in heavily pretreated HL patients, including some cases who relapsed after HDCT. The duration of many of the responses however was short and the treatment was commonly associated with significant hematological toxicity. For HL patients treated with a reduced intensity allogeneic transplant, the treatment related mortality at 1 year was approximately 20%, and the 2 year overall survival was 50%.[91] The treatment related mortality and overall survival was significantly worse for older patients. However, the use of haploidentical transplantation with administration of cyclophosphamide post- transplant has resulted in less graft vs host disease, and a lower relapse risk in HL patients.[92] In patients with relapsed or refractory nodular lymphocyte predominant HL and other multiple relapsed CD20-positive cases of HL, studies of rituximab have shown high response rates, but unfortunately these have been of short duration.[93,94]

Brentuximab vedotin, an antibody drug conjugate targeting CD30, is an established therapy in HL patients who have relapsed post-transplant. The initial studies testing this agent were conducted in this patient population, and the phase I and II clinical trials of brentuximab vedotin showed significant clinical activity.[92] In the pivotal phase II trial of 102 patents with HL that had failed an ASCT, an ORR of 75% was seen with a CR rate of 34%. The median duration of response was 47 weeks and the agent was relatively well tolerated.[95] The median duration of response for those in CR was 20.5 months.

More recently, clinical trials have shown that blocking interactions between the cell surface receptor programmed cell death 1 (PD-1), and its ligands PD-L1 and PD-L2 results in very high clinical response rates (Table 1). In an initial clinical trial using nivolumab, 23 patients with relapsed and refractory Hodgkin lymphoma received nivolumab every other week.[100] Most patients had previously received brentuximab vedotin and an autologous stem cell transplant. In this cohort of patients, a response rate of 87% was seen with 17% complete responses. With longer-term follow-up, almost half of the patients in the study remained on therapy, suggesting that responses to treatment are durable. A second clinical trial using a different anti-PD-1 monoclonal antibody, pembrolizumab, reported similarly promising results.[101] Thirty-one patients in this study received pembrolizumab every 2 weeks. This patient cohort was also heavily pre-treated with the majority of patients previously receiving an autologous stem cell transplant or brentuximab vedotin. In this trial, the overall response rate was 65% with complete remissions seen in 16% of patients.

Confirmatory phase 2 studies have been performed in Hodgkin lymphoma using both pembrolizumab and nivolumab.[102,103] The phase 2 trial of pembrolizumab in Hodgkin lymphoma (KEYNOTE-087) confirmed the overall response rate in relapsed and refractory patients post-transplant to be 69%.[102] The response rate seen with pembrolizumab were similar in patients with primary refractory disease to those relapsing after multiple lines of therapy.[102] In the phase 2 trial of nivolumab, similar results were seen in Hodgkin lymphoma patients post-transplant, who were either brentuximab vedotin-failures or brentuximab vedotin-naïve, with responses seen in 66% of patients.[103] In both studies, responses have been durable with long-term follow up.[96,97]

Recently, two additional anti-PD-1 antibodies have been tested in patients with relapsed and refractory HL. In a study of 96 patients treated with sintilimab, 74 of 92 evaluable patients (80.4%) had an objective response.[98] Similarly, tislelizumab was tested in a phase 2 study. Of 70 patients treated, 61 (87.1%) achieved an objective response, with 44 (62.9%) achieving a complete response.[99] Anti-PD-1 therapy has also been used in patients who progressed after allogeneic transplantation, and a high response rate has been seen, however, exacerbation of graft vs host disease has been life threatening in a subset of patients.[104,105]

Other promising approaches in this patient population include combination strategies, chimeric antigen receptor (CAR) T-cell therapy, and new antibody drug conjugates. Brentuximab vedotin has been combined with two checkpoint inhibitors, nivolumab and ipilimumab, and the triplet combination resulted in an ORR of 95% and a CR rate of 84%.[106] Note, CAR T-cell therapy is still very early in development, but has been shown to be safe with promising clinical activity.[107] In a small study of 18 patients, seven achieved a partial

TABLE 1 Select phase 2 single agent clinical trial results with anti-PD-1 antibodies in patients with relapsed and refractory Hodgkin lymphoma

Agent	Number of patients treated	Overall response rate	Complete response rate	Progression- free survival (PFS)	Reference
Pembrolizumab	210	71.9%	27.6%	Median PFS – 13.7 months	96
Nivolumab	243	69%	16%	Median PFS – 14.7 months	97
Sintilimab	96	80.4%	34%	6-month PFS – 77.6%	98
Tislelizumab	70	7.1%	62.9%	9-month PFS – 74.5%	99

remission and six achieved stable disease.[108] Finally, ADCT-301 (camidanlumab tesirine (Cami-T)) is an antibody drug conjugate comprising a human monoclonal antibody against CD25 conjugated to a potent pyrrolobenzodiazepine dimer (PBD) toxin. In a phase 1 trial of 60 patients, promising activity was seen.[109] In patients treated at the 45 μg/kg dose, the ORR was 80.8% (21/26 pts) and the CR rate was 50% suggesting encouraging clinical activity.

5 | SUMMARY

Optimal management of patients with HL requires an accurate diagnosis and careful staging of the disease. Identification of poor prognostic features then allows for risk-adapted therapy to potentially increase the likelihood of cure and minimize toxicity. Future directions to further improve the outcome of patients with HL will include incorporating into frontline therapy additional agents that are effective in the relapsed setting.

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