Hodgkin Lymphoma: Diagnosis and Treatment

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Abstract

Hodgkin lymphoma is a rare B-cell malignant neoplasm affecting approximately 9000 new patients annually. This disease represents approximately 11% of all lymphomas seen in the United States and comprises 2 discrete disease entities—classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma. Within the subcategorization of classical Hodgkin lymphoma are defined subgroups: nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich Hodgkin lymphoma. Staging of this disease is essential for the choice of optimal therapy. Prognostic models to identify patients at high or low risk for recurrence have been developed, and these models, along with positron emission tomography, are used to provide optimal therapy. The initial treatment for patients with Hodgkin lymphoma is based on the histologic characteristics of the disease, the stage at presentation, and the presence or absence of prognostic factors associated with poor outcome. Patients with early-stage Hodgkin lymphoma commonly receive combined-modality therapies that include abbreviated courses of chemotherapy followed by involved-field radiation treatment. In contrast, patients with advanced-stage Hodgkin lymphoma commonly receive a more prolonged course of combination chemotherapy, with radiation therapy used only in selected cases. For patients with relapse or refractory disease, salvage chemotherapy followed by high-dose treatment and an autologous stem cell transplant is the standard of care. For patients who are ineligible for this therapy or those in whom high-dose therapy and autologous stem cell transplant have failed, treatment with brentuximab vedotin is a standard approach. Additional options include palliative chemotherapy, immune checkpoint inhibitors, nonmyeloablative allogeneic stem cell transplant, or participation in a clinical trial testing novel agents.

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In 2015, approximately 9050 new cases of Hodgkin lymphoma will be diagnosed in the United States.[1] Hodgkin lymphoma has a bimodal disease distribution, with an increased incidence in patients in their teenage years or early 20s and a similar increased incidence in patients older than 55 years.[2] The exact cause of Hodgkin lymphoma remains unknown, but factors associated with an increased risk for Hodgkin lymphoma include exposure to viral infections, familial factors, and immunosuppression. Siblings of patients with Hodgkin lymphoma have an increased risk for this disease,[3,4] and a twin of a patient with Hodgkin lymphoma is also at substantially increased risk.[5,6]

Although familial factors may suggest a genetic cause for Hodgkin lymphoma, multiple studies have also suggested that an abnormal immune response to infection may play a role in the pathogenesis of Hodgkin lymphoma. Epstein-Barr virus has been implicated in the etiology of Hodgkin lymphoma in multiple epidemiological and serologic studies, and the Epstein-Barr virus genome has been detected in tumor specimens in certain trials.[7] Furthermore, patients with human immunodeficiency virus infection are at considerably increased risk of Hodgkin lymphoma compared with the general population.[8] Patients with immunosuppression associated with human immunodeficiency virus commonly present with more advanced stage of the disease in unusual sites and have a poorer prognosis after initial treatment.[9,10] In contrast, studies have found that infections such as chickenpox, measles, mumps, rubella, and pertussis in childhood are in fact inversely associated with the risk of Hodgkin lymphoma and may be protective.[11]

Advances in therapy have substantially increased the likelihood of cure for patients with Hodgkin lymphoma. Currently, more than 80% of patients with newly diagnosed Hodgkin lymphoma are likely to be cured of their disease. Some subsets of patients still have a poorer prognosis, however, particularly patients who are elderly when they present with Hodgkin lymphoma. Although many patients have a good outcome, approximately 1150 deaths from Hodgkin lymphoma occur annually in the United States.[12]

DIAGNOSIS OF HODGKIN LYMPHOMA

Most patients with Hodgkin lymphoma present with supradiaphragmatic lymphadenopathy. Retroperitoneal and inguinal lymphadenopathy occur less frequently. Approximately one-third of patients present with constitutional symptoms. These symptoms include high fevers, drenching night sweats, and profound weight loss. Patients may also present with chronic pruritus. Although it is more common for the disease to involve regional lymph nodes, Hodgkin lymphoma may also involve extranodal sites either by direct invasion or hematogenously. Common sites that may be involved include the spleen, liver, lungs, and bone marrow.

In patients with Hodgkin lymphoma, a definitive diagnosis is critical and requires that the treating physician provide the pathologist with an adequate pathologic specimen. Fine-needle aspiration or core-needle biopsy specimens are commonly inadequate because they do not represent the architecture of the lymph node and therefore preclude an accurate diagnosis. Hodgkin lymphoma has the unique characteristic of malignant cells constituting only a minority of the intratumoral cell population, and therefore, a small biopsy specimen may not include sufficient malignant cells.[13] To establish a definitive diagnosis, it is necessary to identify Reed-Sternberg cells within the biopsy specimen. These cells are commonly seen within a rich cellular environment composed of reactive lymphocytes, eosinophils, and histiocytes. Two distinct disease entities have been defined in Hodgkin lymphoma, the commonly diagnosed classical Hodgkin lymphoma and the uncommon nodular lymphocyte-predominant Hodgkin lymphoma.[14] Within the category of classical Hodgkin lymphoma, 4 subgroups have been identified: nodular sclerosis Hodgkin lymphoma, mixed cellularity Hodgkin lymphoma, lymphocyte depletion Hodgkin lymphoma, and lymphocyte-rich Hodgkin lymphoma.

The pathologic hallmark of classical Hodgkin lymphoma is the presence of large malignant multinucleated Reed-Sternberg cells, which are present within a characteristic reactive cellular background. Each subtype of Hodgkin lymphoma has distinct clinical features. Nodular sclerosis subtype tends to affect adolescents and young adults. Most commonly, this subtype presents with localized disease often involving the mediastinum and supraclavicular or cervical lymph nodes. In contrast, mixed cellularity Hodgkin lymphoma is more prevalent either in children or elderly persons, commonly presents

with advanced-stage disease, and sometimes has a poorer prognosis. Lymphocyte depletion Hodgkin lymphoma is reported less frequently than it was previously because many of the previously reported cases are now reclassified as non-Hodgkin lymphomas. This subtype often occurs in elderly patients and is commonly associated with AIDS. These patients often present with extensive extranodal disease without substantial lymphadenopathy. Lymphocyte-rich classical Hodgkin lymphoma has an appearance similar to nodular lymphocyte-predominant Hodgkin lymphoma (discussed in the next paragraph), but Reed-Sternberg cells are identified with a more classical immunophenotype consistent with classical Hodgkin lymphoma rather than nodular lymphocyte-predominant Hodgkin lymphoma.[15]

Nodular lymphocyte-predominant Hodgkin lymphoma is a unique pathologic entity that is distinct from classical Hodgkin lymphoma. This entity lacks typical Reed-Sternberg cells but instead has a neoplastic population of large cells known as *lymphocytic and histiocytic (L&H) cells*. These cells typically express CD20 and are usually negative for CD30, in contrast with classical Hodgkin lymphoma.[16] Nodular lymphocyte-predominant Hodgkin lymphoma is more frequent in males and may present with limited nodal disease often involving the neck but often sparing the mediastinum. The clinical course of nodular lymphocyte-predominant Hodgkin lymphoma differs from that of classical Hodgkin lymphoma in that the disease has a more indolent course but displays a propensity for late relapses.[17] Transformation to a more aggressive histology such as diffuse large B-cell lymphoma may occur in a subset of patients.

STAGING AND PROGNOSTIC FACTORS

An accurate determination of disease stage in patients with Hodgkin lymphoma is vital to selection of the appropriate initial treatment. The staging system for Hodgkin lymphoma is based on the location of lymphadenopathy, the number and size of lymph node sites, and whether the extranodal lymph node involvement is contiguous or due to dissemination of the disease systemically. Constitutional symptoms (also called *B symptoms*) are also incorporated into the standard staging classification. Positron emission tomography (PET) has recently emerged as an important tool for optimizing the staging of Hodgkin lymphoma. The use of PET adds considerably to staging information that previously was obtained by more standard radiologic methods.[18]

The goal of treatment for patients with Hodgkin lymphoma is to cure the disease but limit long-term complications. The use of factors that identify patients who are at high risk for relapse is critical in defining the optimal intensity and duration of treatment. This process ensures adequate treatment and avoids overtreatment for some patients or undertreatment for others. Prognostic factors are defined by whether the patients have early-stage or advanced-stage disease. Prognostic factors for patients with early-stage Hodgkin lymphoma include the presence of a bulky mediastinal mass, an increased sedimentation rate, multiple nodal site involvement, involvement of extranodal sites, age greater than 50 years, and substantial enlargement of the spleen.[19,20] In contrast, prognostic factors for patients with advanced-stage disease focus less on disease bulk and more on evidence of systemic involvement. The International Prognostic Factors Project on Advanced Hodgkin's Disease[21] identified 7 variables for patients with advanced disease: (1) age greater than 45 years, (2) stage IV disease, (3) male sex, (4) white blood cell count greater than 15,000/μL (to convert to $\times 10^9$/L, multiply by 0.001), (5) lymphocyte count less than 600/μL (to convert to $\times 10^9$/L, multiply by 0.001), (6) albumin level less than 4.0 g/dL (to convert to g/L, multiply by 10.0), and (7) hemoglobin value less than 10.5 g/dL (to convert to g/L, multiply by 10.0). Use of these factors confirmed that they predict patient outcome in a multivariate analysis. In the high-risk category of patients with 5 or more of these prognostic factors, the 5-year freedom from progression was only 42%. In contrast, patients with no poor prognostic factors had an 84% likelihood of remaining disease free at 5 years.

TREATMENT OF HODGKIN LYMPHOMA

In determining the optimal treatment for patients with Hodgkin lymphoma, the factors that play a major role include the histologic features of the disease (classical Hodgkin lymphoma compared with nodular lymphocyte-predominant Hodgkin lymphoma), the stage of the disease (particularly whether the patient has early- or advanced-stage disease), the presence of clinical factors that

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suggest a poor prognosis, the presence of systemic symptoms, and the presence or absence of a bulky mass, defined as a single site of disease greater than 10 cm in diameter.

[^{18}F]-Fludeoxyglucose (FDG)—PET also plays a key role in defining the initial treatment. It is particularly important in confirming the stage of the disease and is also used to determine treatment success. While treatment is being given, an interim PET scan (typically done after 2 cycles of therapy) that is positive (indicating no or suboptimal response to treatment) may result in intensification of treatment, whereas treatment may be decreased if PET is negative (indicating response to therapy). Clinical trials are currently under way to determine whether this approach impacts patient outcome. A positive PET scan at the end of therapy may result in the addition of involved-field radiation therapy to PET-positive sites of disease. An increasingly positive PET result at any point during treatment may suggest progressive disease or chemotherapy-resistant disease, and repeated biopsy of the PET-positive sites to confirm this evidence is always recommended. The use of PET to define treatment is based on previous studies documenting that FDG-positive PET on completion of treatment is associated with a higher risk of disease recurrence regardless of imaging findings.[22,23] Furthermore, findings on interim PET after 2 cycles of treatment have been reported to be predictive of progression-free survival and overall survival in patients with Hodgkin lymphoma. In fact, PET findings are a better predictor of outcome than other prognostic factors including stage of disease, presence of extranodal sites of disease, and other prognostic factors.[24,25]

Initial Treatment

Initial treatment of Hodgkin lymphoma is usually different for 3 subgroups of patients, namely, patients with early-stage disease with favorable prognostic factors, patients with limited-stage disease who have unfavorable prognostic factors, and those with advanced-stage disease. In general, patients with early-stage disease receive shorter courses of combination chemotherapy followed by involved-field radiation therapy. In contrast, patients with advanced-stage disease typically receive more prolonged courses of chemotherapy, and radiation is added only in selected cases.

Early-Stage Hodgkin Lymphoma With Favorable Prognostic Factors. The management of early-stage Hodgkin lymphoma (stages I-IIA) has evolved over recent years. Initially, treatment with extended-field radiation therapy was considered standard. Because of the high likelihood of relapse and increased long-term complications, extended-field radiation therapy is no longer used.[26] A randomized trial comparing subtotal nodal radiation therapy with or without ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy found that patients being treated with subtotal nodal radiation therapy had an inferior overall survival and a higher rate of causes of death other than Hodgkin lymphoma when compared with those who received ABVD chemotherapy alone.[27] Therefore, patients are most commonly treated with chemotherapy for control of any distant areas involved by Hodgkin lymphoma, and chemotherapy is combined with involved-field radiation therapy restricted to sites of confirmed disease involvement.

Most patients with early-stage Hodgkin lymphoma and favorable prognostic factors will commonly receive 2 to 4 cycles of combination chemotherapy and then undergo involved-field radiation therapy at a dose of approximately 20 to 35 Gy.[28] Data from a 4-arm clinical trial performed by the German Hodgkin Study Group (GHSG) revealed that patients with favorable prognostic factors may in fact benefit from less therapy.[29] The study of 1370 patients compared 2 cycles with 4 cycles of ABVD chemotherapy and also compared 20 Gy with 30 Gy of involved-field radiation therapy. There was no difference in response to therapy, progression-free survival, or overall survival for any of the 4 treatment groups. Therefore, ABVD chemotherapy for 2 cycles followed by 20-Gy involved-field radiation therapy is the current standard for patients with early-stage Hodgkin lymphoma who have favorable prognostic factors.[29] However, a variety of clinical trials are currently in progress to determine whether radiation therapy is in fact required. Initial studies have suggested that patients who are PET negative after 3 cycles of treatment may in fact not require any radiation

therapy at all.[30] Further trials are also under way to consider using agents such as brentuximab vedotin instead of radiation therapy as consolidation therapy after the initial 2 to 3 cycles of ABVD chemotherapy.

Early-Stage Hodgkin Lymphoma With Unfavorable Prognostic Factors. In patients with unfavorable prognostic factors including multiple nodal sites, evidence of extranodal disease, or a bulky mediastinal mass, combination chemotherapy followed by involved-field radiation therapy is also the treatment of choice. In general, however, these patients will commonly receive at least 4 cycles of combination chemotherapy (often using more intensive regimens) followed by involved-field radiation therapy.[31,32] Data to support this approach include the results of a clinical trial of 1395 patients with stage I/IIA Hodgkin lymphoma with unfavorable features including a large mediastinal mass, extranodal disease, or an elevated sedimentation rate.[32] In this study, patients were randomized to receive ABVD chemotherapy for 4 cycles of treatment or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) chemotherapy at baseline doses for 4 cycles of treatment with a further comparison of the use of 20-Gy or 30-Gy involved-field radiation therapy. The results revealed that patients receiving ABVD chemotherapy required 30 Gy of involved-field radiation treatment, whereas the outcomes were similar when 20 Gy or 30 Gy of radiation therapy was used in combination with a more intensive regimen such as BEACOPP chemotherapy. Overall, however, the assessment from this study was that ABVD chemotherapy for 4 cycles plus 30 Gy of involved-field radiation therapy is a standard of care for patients with early-stage Hodgkin lymphoma and unfavorable prognostic factors.[32] Further studies have investigated intensifying chemotherapy in this patient group. In a clinical trial performed by the GHSG, patients were randomized to ABVD chemotherapy for 4 cycles or escalated doses of BEACOPP for 2 cycles followed by 2 cycles of ABVD chemotherapy.[33] All patients were then treated with 30 Gy of involved-field radiation treatment. In this study, the freedom from treatment failure analysis favored the more aggressive chemotherapy arm, but there was no difference in overall survival and increased toxicity was seen in the aggressive chemotherapy arm. Additional studies have since examined ways to maintain the efficacy of treatment but decrease potential toxicity.

To achieve this goal, the use of PET has played an important role. [^{18}F]-Fludeoxyglucose—PET has been used as an interim readout of treatment efficacy, and its value has been further enhanced by the use of a 5-point scale to analyze the results.[34] Using these Deauville criteria, FDG uptake greater than that in the mediastinal blood pool is considered positive if treatment is to be decreased or abbreviated. In most other cases, FDG uptake greater than that in the liver at any site is considered positive. The findings on interim PET are now being used in clinical trials to inform decisions concerning intensification or dose reduction of chemotherapy post-PET. Two recently reported studies have illustrated this approach. The United Kingdom National Cancer Research Institute RAPID (Randomised Phase III Trial to Determine the Role of FDG-PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease) study randomized patients with early-stage disease who had negative PET after 3 cycles of ABVD chemotherapy to either receive 30 Gy of involved-field radiation therapy or be observed without additional treatment.[30] This study found that the 3-year progression-free survival and overall survival were not significantly different between the 2 arms. There was, however, a trend toward less disease control in patients who did not receive radiation therapy, and in a subset analysis excluding patients who did not receive treatment as defined by the protocol, this difference became statistically significant. A similar study conducted by the European Organisation for Research and Treatment of Cancer (HD10 study) compared standard therapy with ABVD chemotherapy in combination with involved-field radiation therapy to a nonradiotherapy approach using chemotherapy only.[35] Similar to the RAPID trial, this randomization occurred in patients with negative PET after 2 cycles of ABVD chemotherapy. The results in this study suggested poorer disease control in patients who received chemotherapy only, but a detrimental effect on overall survival has not yet

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been documented and will require longer follow-up.

The evidence to date suggests that the use of combined-modality treatment results in very good disease control for patients with early-stage Hodgkin lymphoma. A notable percentage of patients managed with this approach may in fact be cured. The outcome for patients treated with chemotherapy alone in this population appears quite similar to that with the combined-modality therapy approach, and the use of PET may in the future allow us to identify patients who would benefit from less treatment and possibly avoid complications of radiation treatment.

Advanced-Stage Hodgkin Lymphoma. Patients with stage IIB, III, and IV disease are considered to have advanced-stage lymphoma, and patients in this category are commonly managed with combination chemotherapy alone. Initially, MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) chemotherapy was developed for patients who had relapse after radiation treatment, and this combination was believed to be highly effective.[36] Subsequently, ABVD chemotherapy was developed as a combination for patients with advanced-stage disease, and comparative studies randomizing patients to ABVD chemotherapy and MOPP chemotherapy reported an advantage for patients receiving ABVD chemotherapy.[37-40] To further decrease toxicity, the Stanford V regimen was developed that included many of the active agents from both MOPP and ABVD treatment. The regimen was a brief dose-intensive regimen combined with radiation treatment.[41,42] Initial studies achieved good results with this combination, and numerous clinical trials have compared the Stanford V regimen to ABVD. These trials have generally reported similar response rates and similar failure-free and overall survival.[43-45] The incidence of adverse events has also been similar between the 2 regimens, with patients receiving ABVD at risk for greater lung toxicity and patients receiving the Stanford V regimen having development of a greater number of other toxicities such as hematologic toxicities.

The GHSG has developed a standard-dose and an escalated-dose BEACOPP for patients with advanced-stage Hodgkin lymphoma.[46] Initial trials compared cyclophosphamide, vincristine, procarbazine, and prednisone alternating with ABVD to escalated- and standard-dose BEACOPP.[47] These studies found better tumor control and overall survival for patients receiving dose-escalated BEACOPP.[48] Other randomized trials comparing ABVD chemotherapy and BEACOPP chemotherapy in advanced-stage Hodgkin lymphoma have also been reported.[49-51] These studies have revealed improved progression-free survival for patients receiving escalated BEACOPP, and in a meta-analysis of ABVD and escalated BEACOPP, there appeared to be an overall survival advantage for escalated BEACOPP.[52] However, severe adverse events have been more frequent in patients receiving BEACOPP than in ABVD-treated patients, and this has led physicians to question whether all patients need to receive this very intensive approach.[53] When a randomized comparison of ABVD chemotherapy and escalated BEACOPP was analyzed and included a secondary analysis of patients undergoing subsequent salvage treatment, the overall final outcome of patients appeared to be similar. The 7-year rate of freedom from second progression between patients who received escalated BEACOPP and ABVD chemotherapy and then a subsequent stem cell transplant if they had disease progression was the same.[50] It may therefore be reasonable to offer less intensive therapy to all patients initially and proceed with salvage treatment and autologous stem cell transplant only for the subset of patients who have disease progression. This plan prevents all patients from receiving intensive initial treatment such as escalated BEACOPP.

Although most of the strategies discussed thus far have focused on intensification of treatment, more recent approaches have focused on adding novel new agents to standard chemotherapy. Clinical trials incorporating the use of brentuximab vedotin in ABVD chemotherapy found that the addition of brentuximab vedotin did increase pulmonary toxicity.[54] When bleomycin was omitted from the combination and patients were treated with AVD chemotherapy plus brentuximab vedotin, a high response rate was seen without serious pulmonary toxicity. A randomized, controlled phase 3 trial is currently in progress comparing ABVD chemotherapy with AVD chemotherapy plus brentuximab vedotin. The GHSG is similarly exploring the use of modified BEACOPP-like regimens in combination

with brentuximab vedotin. Currently, the combination of brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone is being tested in a phase 2 trial to assess whether the use of brentuximab vedotin can augment the BEACOPP regimen and decrease some of the toxicity.[55]

In summary, ABVD chemotherapy remains the most commonly used treatment for patients with advanced-stage Hodgkin lymphoma in the United States. However, more dose-intensive approaches such as the use of escalated BEACOPP are certainly reasonable in patients with multiple poor prognostic factors. In the future, however, the addition of novel agents including brentuximab vedotin and possibly other immunologically active agents may improve the outcome for patients with advanced-stage disease.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma. This subtype of Hodgkin lymphoma has a very different biology and clinical course.[16] Management of this entity is therefore quite different from the previously described management of other subtypes. In patients with stage IA disease and no major risk factors, removal of the lymph node followed by a watchful waiting approach or the use of involved-field radiation therapy is potentially curative and is all the treatment that may be required. These patients may have prolonged disease-free intervals but are at high risk for late relapses. In patients with more advanced-stage disease, ABVD chemotherapy has commonly been used. Because these cells express CD20, rituximab has been used in combination with ABVD chemotherapy. Rituximab treatment has also been used in patients who have disease progression after initial management.[56,57] However, optimal management of this disease entity is still being explored in ongoing clinical trials.

Management of Disease Relapse

Despite a high likelihood of success with front-line treatment, approximately 5% to 10% of cases of Hodgkin lymphoma may be refractory to the initial chemotherapy and/or radiation therapy. Furthermore, approximately 10% to 30% of patients may experience relapse after initially having a complete response to treatment.[58,59] The typical management of these patients is to proceed with salvage chemotherapy followed by an autologous stem cell transplant. Initial phase 2 clinical trials suggest that high-dose chemotherapy followed by an autologous stem cell transplant produces better long-term disease-free survival than conventional chemotherapy. Typically between 30% and 65% of patients have a good outcome with this approach.[60-62] Two randomized trials have confirmed an improved outcome for patients managed with high-dose therapy and autologous stem cell transplant when compared with salvage chemotherapy.[63,64] In both studies, the 3-year event-free survival for patients undergoing an autologous stem cell transplant was better than 50%. Not all patients, however, are eligible for management with an autologous stem cell transplant. In particular, elderly patients have increased treatment-related mortality when managed with an aggressive approach.[65] These patients may benefit instead from the use of agents such as brentuximab vedotin or could be considered for treatment in a clinical trial testing new agents.

Therapeutic Options for Disease Progression After Autologous Stem Cell Transplant

Patients who have disease progression after undergoing an autologous stem cell transplant have a poor outcome.[66] In the past, many of these patients were treated with palliative chemotherapy including agents such as vinorelbine and gemcitabine.[67,68] Many of these patients are also considered for an allogeneic stem cell transplant.[69] The toxicity associated with a myeloablative allogeneic stem cell transplant in this population has been substantial, and therefore, reduced-intensity allogeneic transplant has been preferred.[70] The treatment-related mortality at 1 year with reduced-intensity allogeneic transplant is approximately 20%, with a 2-year overall survival of approximately 50%.[69]

Recent trials have utilized brentuximab vedotin, an antibody drug conjugate targeting CD30 that is expressed predominantly in Reed-Sternberg cells, and this agent has been highly effective.[71] In the initial pivotal phase 2 trial in patients with Hodgkin lymphoma who had disease progression after an autologous stem cell transplant, the overall survival was 75%, with complete responses seen in 34%.[72] A subset of responding patients have had durable remissions with this treatment. Other agents that have shown promise have included histone deacetylase inhibitors, mTOR (mammalian target of

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rapamycin) inhibitors, and immunomodulatory agents.[73-75] Recently, data has been presented from patients who had disease progression after an autologous stem cell transplant and who were treated with an antibody blocking programmed cell death protein 1 (PD-1).[76] Programmed cell death protein 1 is present on intratumoral T cells, and the ligand for PD-1 is highly expressed in Reed-Sternberg cells. Clinical trials utilizing nivolumab and pembrolizumab revealed very high response rates, and many of these responses have been durable.

CONCLUSION

The optimal management of patients with Hodgkin lymphoma requires that an accurate diagnosis be made and that the disease be carefully staged so that optimal treatment can be recommended. Prognostic factors allow for further risk stratification to allow for less therapy for those with good prognostic factors and more intensive treatment for those with poorer prognostic features. Patients with more extensive disease benefit from a more intensive approach, and patients with evidence of disease relapse are managed with autologous stem cell transplant. The future, however, is likely to include new agents that have activity in disease relapse. These treatments include brentuximab vedotin as well as PD-1 blockade in the salvage and front-line setting.

Abbreviations and Acronyms: **ABVD** = doxorubicin, bleomycin, vinblastine, dacarbazine; **BEACOPP** = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; **FDG** = [^{18}F]-fludeoxyglucose; **GHSG** = German Hodgkin Study Group; **MOPP** = nitrogen mustard, vincristine, procarbazine, prednisone; **PD-1** = programmed cell death protein 1; **PET** = positron emission tomography

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