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Hodgkin Lymphoma, Version 2.2015:

Clinical Practice Guidelines in Oncology

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Abstract

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. Classical Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma are the 2 main types of HL. CHL accounts for most HL diagnosed in the Western countries. Chemotherapy or combined modality therapy, followed by restaging with PET/CT to assess treatment response using the Deauville criteria (5-point scale), is the standard initial treatment for patients with newly diagnosed CHL. Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has produced encouraging results in the treatment of relapsed or refractory disease. The potential long-term effects of treatment remain an important consideration, and long-term follow-up is essential after completion of treatment.

Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older. In 2015, an estimated 9,050 people will be diagnosed with HL in the United States and 1,150 people will die of the disease.[1] The WHO classification divides HL into 2 main types: classical Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).[2] CHL is characterized by the presence of Reed-Stern-berg cells in an inflammatory background, whereas NLPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocyte-predominant cells, sometimes termed *popcorn cells*.

The past few decades have seen significant progress in the management of patients with HL; it is now curable in at least 80% of patients. The advent of more effective treatment options has improved the 5-year survival rates that are unmatched in any other cancer within the past 4 decades. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) discuss the clinical management of patients with CHL and NLPHL, focusing exclusively on patients from postadolescence through the seventh decade of life who do not have serious

intercurrent disease. The portion of the guidelines discusses the recommendations outlined in the NCCN Guidelines for the management of CHL. For the complete and most updated version of these guidelines, visit NCCN.org.

Staging and Prognosis

Staging for HL is based on the Ann Arbor staging system.[3,4] Patients with HL are usually classified into 3 groups: early-stage favorable (stage I–II with no unfavorable factors); early-stage unfavorable (stage I–II with any of the unfavorable factors, such as large mediastinal adenopathy, >2–3 nodal sites of disease, B symptoms, numerous sites of disease, or significantly elevated erythrocyte sedimentation rate [ESR] of ≥50); and advanced-stage disease (stage III–IV).

The early-stage unfavorable factors are based largely on the definition of unfavorable prognostic groups from the clinical trials conducted by the EORTC, German Hodgkin Study Group (GHSG), and the National Cancer Institute of Canada (NCIC).[5,6] The NCCN unfavorable factors for stage I–II disease include bulky mediastinal disease (mediastinal mass ratio >0.33) or bulky disease greater than 10 cm, B symptoms, ESR greater than 50, and more than 3 nodal sites of disease.

The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis.[7] The IPS helps to determine the clinical management and predict prognosis for patients with stage III–IV disease.[7]

Response Criteria

Clinical management of patients with CHL involves initial treatment with chemotherapy or combined modality therapy, followed by restaging at the completion of chemotherapy to assess treatment response. Assessment of response to initial treatment is essential because the need for additional treatment is based on the treatment response.

The International Working Group (IWG) published the guidelines for response criteria in 1999.[8] In 2007, the IWG guidelines were revised by the International Harmonization Project (IHP) to incorporate immunohistochemistry, flow cytometry, and PET scans in the definition of response.[9,10] The IHP response criteria were initially developed for the interpretation of PET scans at the completion of treatment. In recent years, these criteria have also been used for interim response assessment.[11]

In 2009, the Deauville criteria were defined for the interpretation of interim and end-of-treatment PET scans based on the visual assessment of FDG uptake in the involved sites. These criteria use a 5-point scale (5-PS) to determine the FDG uptake in the involved sites relative to that of the mediastinum and the liver.[12–14] In the 5-PS (Deauville criteria), scores 1 to 4 refer to initially involved sites, and score 5 refers to an initially involved site and/or new lesions related to lymphoma.[12,13] PET scans with a score of 1 or 2 are considered “negative,” and PET scans with a score of 4 and 5 are considered “positive.”[15] In some situations, a score of 3 may be considered negative; however, for deescalation of therapy based on interim PET scans, a threshold for positivity that includes a score of 3 using the

mediastinal blood pool uptake as the reference is appropriate (PET scans with a score of 1–2 are considered negative and PET scans with a score of 3–5 are considered positive).[16] The 5-PS (Deauville criteria) has been validated in international multicenter trials for PET-guided interim response assessment and risk-adapted therapy in patients with HL.[17–21]

Role of PET Scans

PET imaging and, more recently, integrated PET and CT (PET/CT, hereafter referred to as *PET*) has become an important tool for initial staging and response assessment at the completion of treatment in patients with HL.[11,14] In a recent meta-analysis, PET scans showed high positivity and specificity when used to stage and restage patients with lymphoma.[22] PET positivity at the end of treatment has been shown to be a significant adverse risk factor in patients with early-stage and advanced-stage disease.[23–26] PET scans are increasingly being used to assess treatment response during therapy. Interim PET scans may be useful to identify a subgroup of patients with early-stage disease that can be treated with chemotherapy alone.

An integrated PET scan plus a diagnostic CT is recommended for initial staging, although a separate diagnostic CT is not needed if it was part of the integrated PET scan. Based on the recent findings, the panel consensus was to incorporate the Deauville criteria (5-PS) for interim response assessment with PET scans. The NCCN Guidelines emphasize that the value of interim PET scans remains unclear for many clinical scenarios, and all measures of response should be considered in the context of management decisions.

The role of PET in posttherapy surveillance remains controversial, and further studies are needed to determine its role. Until those studies are completed, PET scans are not recommended for routine surveillance because of the risk of false-positive findings and unnecessary diagnostic interventions and/or radiation exposure.[18,27–30]

Principles of Radiation Therapy

Radiation therapy (RT) can be delivered with photons, electrons, or protons, depending on clinical circumstances. Advanced RT techniques emphasize tightly conformal doses and steep gradients next to normal tissues, and therefore target definition and delineation and treatment delivery verification require careful monitoring (see HODG-C, page 567). Initial diagnostic imaging with contrast-enhanced CT, MRI, PET, ultrasound and other imaging modalities facilitate target definition. Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (eg, lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue, salivary glands) can be achieved with advanced RT planning and delivery techniques, such as 4-dimensional CT simulation, intensity-modulated RT, image-guided RT, respiratory gating, or deep inspiration breath hold.[31,32] These techniques offer significant and clinically relevant advantages in specific instances to spare organs at risk and decrease the risk of normal tissue damage and late effects without compromising the primary goal of local tumor control.[33–39]

Randomized prospective studies to test these concepts are unlikely to be performed, because these techniques are designed to decrease late effects, which usually develop 10 or more

years after completion of treatment. Therefore, the NCCN Guidelines recommend that RT delivery techniques that are found to best reduce the doses to the organs at risk in a clinically meaningful manner without compromising target coverage should be considered in these patients, who are likely to enjoy long life expectancies after treatment.

Treatment Guidelines

Diagnosis and Workup

Core needle biopsy may be adequate for diagnosis, but the panel recommends that excisional lymph node biopsy generally be performed (see HODG-1, page 556).

The role of fine-needle aspiration biopsy in the diagnosis of lymphoma is still controversial.[40–42] Fine-needle aspiration biopsy is considered to be adequate along with immunohistochemistry only when it is called diagnostic of HL by an expert hematopathologist or cytopathologist. Immunostaining for CD3, CD15, CD20, CD30, and CD45 is recommended for CHL.

Workup should include a thorough history and physical examination; standard laboratory tests; PET/CT; and diagnostic contrast-enhanced CT. A chest radiograph is encouraged for patients with a large mediastinal mass. In patients with newly diagnosed HL undergoing pretreatment staging with PET/CT, routine bone marrow biopsy is not required if the PET scan is negative or displays a homogenous pattern of bone marrow uptake.[43] An adequate bone marrow biopsy should be performed if the PET scan displays multifocal (three or more) skeletal lesions or if cytopenias are present.

Evaluation of ejection fraction is recommended for most patients undergoing doxorubicin-based chemotherapy. HIV and hepatitis B testing should be encouraged for patients with risk factors for HIV or unusual disease presentations. Pulmonary function tests, including the test of the diffusion capacity of the lungs for carbon monoxide, are recommended for patients receiving bleomycin-based chemotherapy. Haemophilus influenzae (H-flu), pneumococcal, and meningococcal vaccines are recommended if splenic RT is contemplated. A neck CT scan is also recommended for patients in whom RT to the neck is planned.

A pregnancy test should be performed before women of childbearing age undergo treatment.[44] The guidelines recommend fertility preservation (semen cryopreservation in male patients, ovarian tissue or oocyte cryopreservation in female patients) before the initiation of chemotherapy with alkylating agents or pelvic RT.[45,46] Oophoropexy should be considered to preserve ovarian function in premenopausal women if pelvic RT is contemplated.[47]

Stage I–II Favorable Disease

RT alone was a standard treatment option for patients with early-stage HL for many decades.[48] However, the potential long-term toxicity of high-dose, large-field irradiation includes an increased risk for heart disease, pulmonary dysfunction, and secondary cancers.[49] With the incorporation of chemotherapy regimens routinely used in advanced disease (ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine] and Stanford V) into

the management of patients with early-stage disease, combined modality therapy has replaced RT alone as the treatment of choice for patients with early-stage, favorable disease.

The ABVD regimen was developed as an alternative to MOPP (mechlorethamine, vincristine, prednisone, and procarbazine).[50] The Stanford V regimen is a brief but dose-intensive regimen with significantly fewer cumulative doses of doxorubicin and bleomycin than those used in ABVD, BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone], or other hybrid regimens, thereby reducing the risks of chemotherapy-related infertility, secondary neoplasms, and cardiac and pulmonary toxicity.[51,52] RT is an integral part of the Stanford V regimen.[53]

Bonadonna et al[50] initially established the safety and efficacy of ABVD (4 cycles) followed by 36 Gy of involved-field RT (IFRT) as the standard treatment for patients with early-stage disease. The HD10 trial investigated the reduction of the number of cycles of ABVD and the IFRT dose in patients with stage I–II disease with no risk factors.[54] Patients were not eligible if they had 3 or more sites of disease, any E lesions, bulky mediastinal adenopathy, an ESR greater than 50, or an ESR greater than 30 in conjunction with B symptoms. In this trial, 1370 patients were randomized to 1 of the 4 treatment groups: 4 cycles of ABVD followed by 30 Gy or 20 Gy of IFRT, or 2 cycles of ABVD followed by 30 or 20 Gy of IFRT.[54] The final analysis of this trial showed (with a median follow-up of 79–91 months) no significant differences between 4 and 2 cycles of ABVD in terms of rates of 5-year OS (97.1% and 96.6%), freedom from treatment failure (FFTF; 93.0% vs 91.1%), and progression-free survival (PFS; 93.5% vs 91.2%). With respect to the dose of IFRT, the rates of overall survival (OS; 97.7% vs 97.5%), FFTF (93.4% vs 92.9%), and PFS (93.7% vs 93.2%) were also not significantly different between 30 and 20 Gy of IFRT.[54] More importantly, no significant differences were seen in OS, PFS, and FFTF among the 4 treatment arms. The results of the HD10 study confirm that 2 cycles of ABVD with 20 Gy of IFRT is an effective primary treatment for patients with a very favorable presentation of early-stage disease with no risk factors, thereby minimizing the risk of late effects.

The G4 study conducted by the Stanford and Kaiser hospitals evaluated the efficacy of the abbreviated Stanford V chemotherapy (8 weeks or 2 cycles) followed by IFRT (30 Gy) in patients with nonbulky stage IA or IIA disease.[55] Among the 87 patients included in the study, unfavorable risk factors according to GHSG criteria (>2 nodal sites, ESR ≥50, or extranodal involvement) were present in 42 patients (48%), and 33 patients (33%) had unfavorable characters defined by EORTC criteria (>3 nodal sites, ESR ≥50, mixed cellularity, and age ≥50 years). At a median follow-up of 10.6 years, the estimated 10-year freedom from progression (FFP) rate, disease-specific survival, and OS rates were 94%, 99%, and 94%, respectively. Among patients with GHSG criteria, the FFP rate was 100% for those with favorable disease and 88% for those with unfavorable nonbulky disease. The FFP rate, was 98% and 88%, respectively, for patients with favorable and unfavorable disease according to EORTC criteria. No instances were reported of secondary cancers (acute myeloid leukemia or myelodysplastic syndromes) or late cardiac or pulmonary toxicities.

Chemotherapy with ABVD alone has also been investigated in patients with early-stage nonbulky disease (stage I–II or IIIA).[56–59]

In the Memorial Sloan Kettering Cancer Center (MSKCC) study, 152 patients with stages I, II, and IIIA nonbulky disease were prospectively randomized to ABVD (6 cycles) followed by IFRT or extended-field RT (36 Gy) or ABVD (6 cycles) alone. At 60-month follow-up, no significant differences were seen in rates of complete remission duration (91% vs 87%, respectively; *P*=.61), FFP (86% vs 81%, respectively; *P*=.61), and OS (97% vs 90%, respectively; *P*=.08) among patients treated with ABVD plus radiation and those treated with ABVD alone.[57]

In the multicenter study conducted by the NCIC Clinical Trials Group (HD.6), 405 patients with stage IA or IIA HL were randomized to receive ABVD (4–6 cycles) or subtotal nodal RT with or without ABVD.[58] Among patients assigned to RT, those who had a favorable risk profile received subtotal nodal RT alone, and those with any of the adverse prognostic factors (high ESR, age >39 years, mixed cellularity or lymphocyte-depleted histology, or ≥4 nodal sites) were treated with 2 cycles of ABVD followed by subtotal nodal RT. At a median follow-up of 12 years, the OS rate was higher among patients treated with ABVD alone than those treated with subtotal nodal RT with or without ABVD (94% vs 87%; *P*=.04).[59] However, ABVD alone was associated with a lower rate of FFP than subtotal nodal RT with or without ABVD (87% vs 92%; *P*=.05), and no significant differences were seen in the event-free survival (EFS) rates between the groups (85% and 80%, respectively; *P*=.60). In the subset analysis of patients with a favorable disease, no significant differences were seen between any outcome for patients randomly assigned to subtotal nodal RT alone and those assigned to ABVD alone.[59] Among patients with unfavorable risk factors, the 12-year estimated OS rate was higher among patients in the ABVD-only group than among the patients who received subtotal nodal RT plus ABVD (92% vs 81%, respectively; *P*=.04), whereas the FFP rate was lower in the ABVD-only group (86% vs 94%; *P*=.006) and no significant differences were seen in the 12-year EFS rate (83% vs 78%; *P*=.74) between the groups.[59] Among patients randomized to ABVD alone, the FFP rate was significantly higher among those who achieved a complete remission or complete remission, unconfirmed (based on CT) after 2 cycles of ABVD than among those who did not achieve a complete remission (12-year estimated rate of FFP, 94% and 81%, respectively; *P*=.02). This study, however, was closed prematurely because the results of the EORTC H8F study showed excellent outcomes for patients with stage I–II favorable disease treated with chemotherapy and IFRT.[60]

Combined modality therapy (ABVD or Stanford V chemotherapy plus IFRT) is the preferred treatment for patients with stage I–II favorable disease.

ABVD alone could be a reasonable choice of treatment, especially for younger patients who experience a complete remission after 2 cycles (as documented by CT scan) or for those with a Deauville score of 1 to 3 on PET scan after 2 to 4 cycles of ABVD, to avoid the long-term risks of RT.

NCCN Recommendations—Combined modality therapy (ABVD plus ISRT [category 1][54] or Stanford V chemotherapy)[55] or chemotherapy (ABVD alone)[18,58,59] are included as treatment options for patients with stage IA–IIA favorable disease (absence of all NCCN unfavorable risk factors: bulky mediastinal or >10-cm disease, B symptoms, ESR ≥50 and >3 nodal sites of disease) (see HODG-2 and HODG-3; page 557)

In combined modality therapy, ABVD is generally administered for 4 cycles followed by 30 Gy of involved-site RT (ISRT). In patients who fulfill the GHSG criteria for favorable disease (ESR <30 or ESR <50 without B symptoms, no bulky disease or extralymphatic lesions, and <3 sites of nodal disease), 2 cycles of ABVD followed by 20 Gy of ISRT may be sufficient.[54] Stanford V regimen is administered for 8 weeks followed by 30 Gy of ISRT, which is optimally instituted within 3 weeks of completion of chemotherapy.[55] Interim restaging with PET is recommended after 4 cycles of ABVD (after 2 cycles for patients who fulfill the GHSG criteria for favorable disease) or after 8 weeks of Stanford V chemotherapy. Completion of a planned course of ISRT followed by observation is recommended for patients with a Deauville score of 1 to 4. Biopsy is recommended for all patients with a score of Deauville 5 after completion of chemotherapy. ISRT followed by observation is recommended for patients with negative biopsy results, and patients with positive biopsy results should be managed as described for refractory disease.

Among patients treated with chemotherapy alone, ABVD is initially administered for 2 or 3 cycles, followed by interim restaging.

In the NCIC study (HD.6), patients assigned to ABVD alone were restaged with CT after 2 cycles.[58,59] The FFP was superior for patients who achieved a complete remission or complete remission, unconfirmed after 2 cycles of ABVD (compared with those who did not, based on CT criteria) and these patients went on to receive 2 more cycles of ABVD alone (4 total); patients who did not achieve a complete remission or complete remission, unconfirmed received a total of 6 cycles of ABVD. Consistent with the results of the NCIC study (HD.6), the guidelines recommend restaging with a diagnostic CT of areas of initial disease after 2 cycles of ABVD. Two additional cycles of ABVD (total of 4) are recommended for patients with a complete remission or complete remission, un-confirmed on CT, and 4 additional cycles of ABVD (total of 6) are recommended for those with a partial remission on CT. Restaging with PET is recommended for all patients after completion of 4 or 6 cycles of ABVD. Observation is recommended for those with a Deauville score of 1 to 3 on end-of-treatment PET. ISRT is recommended for patients with a Deauville score of 4 on end-of-treatment PET scan.

Two studies from Europe have evaluated the value of interim PET scans in defining the need for IFRT in patients with stage I–II favorable disease (the UK RAPID trial and the EORTC H10 trial).[18,61] However, these trials report somewhat different conclusions. The interim analysis of the EORTC H10 trial (n=1137; 444 patients with stage I–II favorable disease and 693 patients with stage I–II unfavorable disease) showed that combined modality therapy (ABVD + involved-node RT) resulted in fewer early progressions compared with treatment with ABVD alone, even in patients with early-stage favorable disease and negative PET scan findings after 2 cycles of ABVD.[61] The RAPID trial showed that patients with stages IA–

IIA disease with negative PET findings after 3 cycles of ABVD have excellent outcomes.[18] In this study (n=602; 426 patients had negative PET findings after 3 cycles of ABVD), patients with stage IA–IIA favorable disease (no B symptoms or mediastinal bulky disease) and a Deauville score of 1 to 2 on interim PET scan after 3 cycles ABVD were randomized to either IFRT (n=209) or observation (n=211). After a median follow-up of 45.7 months, the estimated 3-year PFS rate was 93.8% for those treated with IFRT compared with 90.7% for those who received no further treatment. The corresponding 3-year OS rates were 97.0% and 99.5%, respectively. The results of the RAPID trial have been published only in abstract form, and additional follow-up data are required to establish the impact of this approach on long-term survival.

Currently, the NCCN Panel has included the option of ABVD (3 cycles) followed by interim re-staging with PET, with a category 2B recommendation. Consistent with the results of the RAPID trial, no further treatment is recommended for patients with a Deauville score of 1 to 2.[18] An additional cycle of ABVD (total of 4) plus ISRT is recommended for those with a Deauville score of 3 to 4.

Biopsy is recommended for all patients with a Deauville score of 5 after completion of treatment with ABVD (3 or 6 cycles). ISRT is recommended for patients with negative biopsy results, and patients with positive biopsy results should be managed as described for refractory disease.

Stage I–II Unfavorable Disease

The HD8 trial investigated the efficacy of IFRT versus extended-field RT (EFRT) in the context of combined modality therapy for patients with early-stage unfavorable HL with one or more risk factors (large mediastinal mass; extranodal disease; splenic involvement; elevated ESR with or without B symptoms; and >2 lymph node areas of involvement).[62] This trial randomized 1204 patients to 4 cycles of chemotherapy (COPP [cyclophosphamide, vincristine, procarbazine, and prednisone] plus ABVD) followed by EFRT or IFRT. RT (30 Gy plus 10 Gy to bulky sites in both arms) was initiated after chemotherapy for all patients without progressive disease. At 5 years of follow-up, FFTF (85.8% for EFRT and 84.2% for IFRT) and OS (90.8% vs 92.4%) were similar for the groups. In contrast, acute side effects, including thrombocytopenia, leukopenias, and gastrointestinal toxicity, were more frequent in the EFRT group. The 10-year follow-up results confirmed the noninferiority of IFRT in terms of FFTF (79.8% vs 79.7%), PFS (79.8% vs 80.0%), and OS (86.4% vs 87.3%).[63] IFRT was also associated with less acute toxicity and fewer secondary malignancies.

The HD11 trial demonstrated that 4 cycles of ABVD followed by 30 Gy of IFRT is an effective treatment option for patients with early stage unfavorable disease.[64] In this study, 1395 patients with stage I–II unfavorable disease (stage IA, IB, or IIA with at least one of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR ≥50 or ESR ≥30 with B symptoms; or 3 or more involved lymph nodes and stage IIB disease with no bulky mediastinal mass or extranodal involvement) were randomized to either ABVD (4 cycles followed by 30 or 20 Gy of IFRT) or standard-dose BEACOPP (4 cycles followed by 30 or 20 Gy of IFRT). BEACOPP was more effective than ABVD when followed by 20 Gy IFRT (5-year FFTF and PFS rates were 86.8% and 87.0%, respectively, for BEACOPP. The

corresponding rates were 81% and 82%, respectively, for ABVD). However, no difference was seen between the 2 regimens when followed by 30 Gy of IFRT (5-year FFTF and PFS were 87% and 88%, respectively, for BEACOPP. The corresponding rates were 85% and 87%, respectively, for ABVD). BEACOPP was also associated with more toxicity than ABVD.

The results of the prospective study conducted by the Stanford group demonstrated the efficacy of Stanford V regimen followed by RT to initially bulky sites for patients with locally extensive and advanced-stage disease.[65] In this study, 142 patients with locally extensive mediastinal stage I or II disease or stage III or IV disease were treated with Stanford V chemotherapy (12 weeks) followed by RT (36 Gy) to initial bulky sites (≥5 cm) or macroscopic splenic disease. With a median follow-up of 5.4 years, the 5-year FFP and OS rates were 89% and 96%, respectively. No patient experienced disease progression during treatment and no treatment-related deaths or secondary leukemia were reported. Among 16 patients who experienced disease relapse, the freedom from second relapse was 69% at 5 years.

Other investigators have also confirmed that the Stanford V regimen is highly effective for locally extensive and advanced HL, with a low toxicity profile, when RT is administered according to Stanford V protocol guidelines.[66_68] In the MSKCC study, 126 patients with either locally extensive or advanced disease were treated with the 12-week Stanford V chemotherapy regimen followed by 36 Gy of IFRT to bulky sites (≥5 cm) and/or to macroscopic splenic disease.[67] The 5- and 7-year OS rates were 90% and 88%, respectively. A totally of 58% of the patients for whom the Stanford V regimen failed underwent successful second-line therapy with high-dose therapy with autologous stem cell rescue (HDT/ ASCR). Aversa et al[66] from another Italian study group also reported similar findings in patients with bulky or advanced disease. The randomized trial conducted by the United Kingdom National Cancer Research Institute Lymphoma Group (Study ISRCTN 64141244) also showed that the efficacies of Stanford V and ABVD were comparable in terms of overall response rate (ORR) and 5-year PFS and OS rates among patients with stage I–IIA bulky disease or other adverse features and those with stage IIB, III, or IV disease. RT was administered in both arms to sites of previous bulky sites (>5 cm) and to splenic deposits.[68] At the median follow-up of 4.3 years, the ORR, 5-year PFS, and 5-year OS rates were 91%, 76%, and 90%, respectively, for ABVD, and were 92%, 74%, and 92%, respectively, for Stanford V.

The phase III Intergroup trial (E2496) also confirmed that there were no significant differences between ABVD and Stanford V in terms of response rates, failure-free survival, OS, and toxicity in patients with locally extensive (stage I–IIA/B and bulky mediastinal disease) and stage III–IV disease.[69] In this trial, 854 patients were randomized to ABVD (n=428; 6–8 cycles plus 36 Gy of RT only for patients with bulky mediastinal disease) or Stanford V (n=426; 12 weeks of chemotherapy plus 36 Gy of RT for sites >5 cm or for macroscopic splenic disease). The primary end point was failure-free survival, defined as the time from randomization to progression, relapse, or death, whichever occurred first. With a median follow-up of 6.4 years, no difference was seen in ORR (clinical complete remission rates were 72.7% for ABVD and 68.7% for Stanford V), OS (88% at 5 years for both ABVD

and Stanford V; *P*=.86), or FFS (74% for ABVD and 71% for Stanford V at 5 years; *P*=.32) between the arms. Toxicity was also similar in both groups. The planned subgroup analysis showed that the outcome of patients with locally extensive disease was significantly better than that of patients with stage III–IV disease.[69] The 3- and 5-year failure-free survival rates were 82% for patients with locally extensive disease. The corresponding survival rates were 71% and 67%, respectively, for patients with stage III–IV disease (*P*=.001). The 5-year OS rates were 94% and 85%, respectively (*P*<.001).

The HD14 trial demonstrated that BEACOPP followed by ABVD and IFRT significantly improved tumor control and PFS in patients with early-stage unfavorable disease (stage IA, IB, or IIA HL with at least one of the following risk factors: bulky mediastinal mass; extranodal involvement; ESR ≥50 [without B symptoms] or ESR ≥30 [with B symptoms]; or ≥3 involved lymph nodes) and stage IIB disease with either of the latter 2 risk factors).[70] In this trial, 1528 patients were randomized to 4 cycles of ABVD (n=765) or 2 cycles of escalated-dose BEACOPP followed by 2 cycles of ABVD (n=763). Chemotherapy was followed by 30 Gy of IFRT in both arms. At a median follow-up of 43 months, the 5-year FFTF rate was 94.8% compared with 87.7% for ABVD (*P*<.001). The 5-year PFS rate was 95.4% and 89.1%, respectively (*P*<.001). The 5-year OS rate was not significantly different between the arms (97.2% and 96.8%, respectively; *P*=.731). The rate of progression or relapse was also lower in patients treated with BEACOPP followed by ABVD (2.5% vs 8.4%; *P*<.001).

These results suggest that ABVD plus 30 Gy of IFRT remains the standard of care for patients with early-stage unfavorable disease. Stanford V (when given as described with RT) or BEACOPP followed by ABVD are acceptable alternatives for some patients.

NCCN Recommendations

Stage I–II (Unfavorable Bulky Mediastinal Disease or Adenopathy >10 cm With or Without B Symptoms): ABVD followed by ISRT (category1)[64] or Stanford V[65,69] or escalated BEACOPP (2 cycles) followed by ABVD (2 cycles) and ISRT for selected patients younger than 60 years[70] are included as options for patients with stage I–II unfavorable bulky disease.

In the HD14 trial that evaluated escalated BEACOPP followed by ABVD and ISRT, patients with bulky disease in combination with either B symptoms or extranodal disease were excluded.[70] These patients are managed as described for stage III–IV disease.

ABVD is initially administered for 4 cycles followed by interim restaging with PET. Patients with a Deauville score of 1 to 3 are treated with ISRT alone or in combination with 2 additional cycles of ABVD (total of 6), and those with a Deauville score of 4 are treated with 2 additional cycles of ABVD (total of 6) with IFRT (see HODG-4; page 558). Biopsy evaluation is recommended for all patients with a Deauville score of 5 after 4 cycles of ABVD. If the biopsy results are negative, patients should receive 2 additional cycles of ABVD (total of 6) with ISRT. Patients with positive biopsy results should be managed as described for refractory disease.

Stanford V is administered for 12 weeks (3 cycles) followed by ISRT (30–36 Gy) for patients with stage I–II bulky mediastinal disease or bulky disease greater than 10 cm and/or B symptoms (see HODG-5; page 559).[65,69] Patients are restaged with PET at the completion of chemotherapy. ISRT for initial sites greater than 5 cm is recommended for all patients with a Deauville score of 1 to 4. ISRT should be instituted within 2 to 3 weeks of completion of chemotherapy. Biopsy is recommended for all patients with a Deauville score of 5 after completion of therapy. ISRT should be given if the biopsy results are negative. Patients with positive biopsy results should be managed as described for refractory disease.

Patients receiving escalated BEACOPP (2 cycles) and ABVD (2 cycles) are restaged after completion of chemotherapy (see HODG-6; page 559). ISRT is recommended for those with a Deauville score of 1 to 4, and biopsy evaluation is recommended for those with a Deauville score of 5. ISRT should be given if the biopsy results are negative. Patients with positive biopsy results should be managed as described for refractory disease.

Stage I–II (Unfavorable Nonbulky Disease)

ABVD is initially administered for 4 cycles followed by interim restaging with PET (see HODG-7; page 560). ISRT or 2 additional cycles of ABVD (total of 6) is recommended for patients with a Deauville score of 1 to 3, and those with a Deauville score of 4 are treated with 2 additional cycles of ABVD alone (total of 6) followed by restaging. ISRT is recommended for those with a Deauville score of 1 to 3 or a Deauville score 4 or 5 with negative biopsy results after completion of 6 cycles of ABVD. Biopsy is recommended for all patients with a Deauville score of 5 after initial treatment with 4 cycles of ABVD. Two additional cycles of ABVD (total of 6) with ISRT is recommended, if the biopsy results are negative. All patients with positive biopsy results should be managed as described for refractory disease.

Stanford V is administered for 12 weeks (3 cycles) followed by ISRT (30 Gy) for patients with stage I–II unfavorable nonbulky disease based on presence of B symptoms.[69] Patients are restaged with PET at the completion of chemotherapy as described previously for patients with stage I to II unfavorable bulky disease (see HODG-5; page 559). Patients with other unfavorable factors (elevated ESR or >3 sites of disease) are treated with 8 weeks of Stanford V plus 30 Gy ISRT followed by restaging as described for stage IA–IIA favorable disease.[55]

Restaging and additional treatment for patients treated with BEACOPP followed by ABVD are similar to the recommendations described previously for patients with stage I to II (unfavorable bulky disease; see HODG-6; page 559).

Stage III–IV

Although chemotherapy is always used for patients with advanced-stage disease, combined modality therapy is the management approach for some treatment regimens, especially for patients with bulky disease, and is used for poor responders to chemotherapy in other treatment regimens.[26,65,69,71]

The landmark randomized trial by the CALGB showed that ABVD alone or alternating with MOPP was superior to MOPP alone in patients with newly diagnosed advanced HL (stage III–IV).[72] ABVD also was less myelotoxic than MOPP, or ABVD alternating with MOPP. These results were confirmed in a large Intergroup study, which compared ABVD with a MOPP/ABV hybrid regimen in 856 patients with advanced HL.[73] The rates of complete remission (76% vs 80%), 5-year FFS (63% vs 66%), and OS (82% vs 81%) were similar for ABVD and MOPP/ABV, respectively. However, MOPP/ABV was associated with a greater risk for acute pulmonary and hematologic toxicity, myelodysplastic syndromes, and leukemia.

Another randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) also confirmed that there was no significant difference in EFS and OS between ABVD and other multidrug regimens in patients with advanced HL. The other multidrug regimens were more toxic than ABVD and were associated with poorer outcomes in older patients.[74] Updated results with a median follow-up of 83 months were consistent with the early results.[75]

ABVD has since been the standard treatment for patients with stage III–IV disease. Stanford V and BEACOPP are the other 2 regimens developed to improve the outcome of patients with advanced disease.

The results from prospective studies conducted by the Stanford group and other investigators have demonstrated the efficacy of Stanford V and IFRT in patients with advanced-stage disease.[65_68] The recently completed phase III Intergroup trial (E2496) also showed that there was no significant difference between ABVD and Stanford V (with RT, when indicated, according to Stanford V protocol guidelines) in terms of ORR, FFS, OS, and toxicity in patients with stage III–IV disease.[69] However, among patients with high risk-disease (IPS ≥3), the 5-year FFS rate was significantly better for ABVD than for Stanford V (67% vs 57%; P=.02), but no significant difference was seen in 5-year OS rate (84% vs 77%; P=.15).

The efficacy of BEACOPP in patients with advanced disease was demonstrated in 2 phase III randomized trials conducted by the GHSG.[76,77] In the HD9 study, 1196 patients with stage IIB and IIIA disease with risk factors or stage IIIB and IV disease were randomized to undergo 8 cycles of COPP ABVD, 8 cycles of standard-dose BEACOPP, or 8 cycles of escalated-dose BEACOPP.[76] Each regimen was followed by RT to initial sites of disease greater than 5 cm. Most patients in each treatment arm had stage III–IV disease. At 5-year analysis, escalated-dose BEACOPP showed better tumor control and OS than COPP ABVD and significantly lower rates of early progression than COPP ABVD or standard-dose BEACOPP. The 10-year analysis confirmed that escalated-dose BEACOPP was significantly better than standard-dose BEACOPP or COPP ABVD in terms of FFTF (82%, 70%, and 64%, respectively) and OS rates (86%, 80%, and 75%, respectively). Escalated-dose BEACOPP was significantly better than standard-dose BEACOPP in terms of FFTF (P<.0001) and OS (P=.0053).[77]

The final results of the HD12 study (n=1670) that compared 8 cycles of escalated-dose BEACOPP with 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP, with or without RT, also confirmed the efficiency of escalated-dose BEACOPP for patients with advanced-stage HL who have risk factors, as reported in the HD9 trial.[78] In this study, at 5 years, the FFTF (86.4% and 84.8%, respectively) and PFS (87.5% and 85%, respectively) were better (although the difference was not significant) for 8 cycles of escalated-dose BEACOPP compared with 4 cycles of escalated-dose BEACOPP followed by 4 cycles of standard-dose BEACOPP. The 5-year OS rate, however, was not different (92% and 90.3%, respectively).[78]

The final analysis of the HD15 trial showed that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT resulted in significantly superior OS and tumor control than 8 cycles of escalated-dose BEACOPP in patients with advanced-stage disease (stage IIB with large mediastinal mass or stage III–IV disease).[26] In this study, 2182 patients were randomly assigned to 1 of the 3 treatment groups: 8 cycles of escalated-dose BEACOPP (n=728), 6 cycles of escalated-dose BEACOPP (n=726), or 8 cycles of a time-intensified standard-dose BEACOPP (n=728). RT (30 Gy) was restricted to patients with PET-positive residual sites (≥2.5 cm) after chemotherapy. The 5-year FFTF rates were 84.4%, 89.3%, and 85.4%, respectively, for the 3 groups. The corresponding OS rates were 91.9%, 95.3%, and 94.5%, respectively, and were significantly better with 6 cycles of escalated-dose BEACOPP than with 8 cycles of escalated-dose BEACOPP (*P*=.019). Escalated-dose BEACOPP was also associated with less treatment-related mortality (4.6% vs 7.5% for 8 cycles of escalated-dose BEACOPP and 5.2% for 8 cycles of time-intensified standard-dose BEACOPP) and fewer secondary cancers (2.4% vs 4.7% for 8 cycles of escalated-dose BEACOPP and 3.1% for 8 cycles of time-intensified standard-dose BEACOPP). These results confirm that 6 cycles of escalated-dose BEACOPP followed by PET-guided RT is an acceptable treatment for patients with advanced-stage disease.

Results from studies that have compared escalated-dose BEACOPP with standard-dose BEACOPP or ABVD failed to show an OS advantage for escalated-dose BEACOPP, although it resulted in better tumor control in patients with advanced disease.[79–82] However, these studies were not sufficiently powered to determine differences in OS due to small patient numbers. The long-term follow-up analysis of the HD2000 trial also showed that the risk of secondary malignancy at 10 years was significantly higher with BEACOPP than with ABVD (6.7 vs 0.9; *P*=.027).[83] The ongoing EORTC 20012 trial is evaluating BEA-COPP (4 cycles of escalated-dose and 4 cycles of standard-dose) and ABVD (8 cycles) in high-risk patients with stage III–IV disease and an IPS of 3 or greater (274 patients in the BEACOPP arm and 275 patients in the ABVD arm).[81] The preliminary results showed no improvement in OS (86.7% and 90.3, respectively, at 4 years; *P*=.208) or EFS (63.7% and 69.3%, respectively, at 4 years; *P*=.312), although the PFS was significantly better with BEACOPP (83.4% vs 72.8% for ABVD; *P*=.005). Early discontinuations were also more frequent with BEACOPP. The median follow-up was 3.8 years.[81] Long-term follow-up is necessary to confirm these preliminary findings.

Several trials have addressed the role of consolidative RT after completion of chemotherapy in patients with stage III–IV disease.

The SWOG multicenter study showed no improvement in OS rates for patients who underwent low-dose IFRT after MOP BAP (mechlorethamine, vincristine, procarbazine plus bleomycin, doxorubicin, and prednisone), but the remission duration was prolonged in several subgroups, especially in patients with bulky nodular sclerosis CHL.[84] In the randomized trial (EORTC 20884 trial) that assessed the role of consolidation RT after MOPP ABV chemotherapy in patients with advanced disease, 739 patients with untreated stage III–IV disease received 6 to 8 cycles of MOPP ABV. Patients showing a complete remission on CT imaging after chemotherapy were randomized to no further treatment or IFRT, and those with a partial remission received IFRT to involved nodal areas and extra-nodal sites.[85] The 8-year OS and EFS rates in the partial remission group were 76% and 84%, respectively. These outcomes were not significantly different in patients with a complete remission (with or without IFRT), suggesting that consolidative IFRT is beneficial for patients experiencing partial remission after chemotherapy.

In the randomized controlled trial from the United Kingdom Lymphoma Group (LY09 trial) that compared ABVD with 2 other multidrug regimens, IFRT was recommended for incomplete response to chemotherapy or bulk disease at presentation.[75] PFS was superior for patients who received RT (5-year PFS was 71% without RT and 86% with RT) and a similar advantage was also seen for OS. The final results of the HD12 trial also showed that consolidation RT was beneficial for patients with residual disease after escalated-dose BEACOPP (FFTF was 90.4% and 87.0%, respectively), whereas this effect was not seen in patients with initial bulk disease who were experiencing complete remission after chemotherapy.[78] In contrast, Laskar et al[86] reported a survival advantage for consolidative RT in patients experiencing complete remission after initial chemotherapy, particularly in patients younger than 15 years and those with B symptoms and bulky and advanced disease. However, this study included patients with a different distribution of histologic subtypes of HL than those included in Western studies, and most patients had early-stage HL. Notably, none of these studies incorporated PET scan in the evaluation of response.

In the HD15 trial, RT (30 Gy) after BEACOPP chemotherapy was restricted to patients experiencing partial remission with PET-positive residual disease (≥2.5 cm). PET-negative patients received no additional RT.[26] Of the 739 qualified patients with residual disease (≥2.5 cm) after 6 to 8 cycles of BEACOPP, 548 (74%) had negative PET results; 191 patients (26%) had positive PET results and received consolidative RT. The final analysis showed that the prognosis of patients in partial remission with PET-negative persistent residual disease after chemotherapy was similar to that of those who were in complete remission as measured by conventional CT (the 4-year PFS rate was 92.1%), suggesting that consolidative RT could be omitted in patients with a PET-negative partial remission.[26] However, the use of consolidative RT was effective for patients with a PET-positive partial remission, because the 4-year PFS rate in this group was 86.2%.

Two recent European trials evaluated the role of HDT/ASCR as a consolidative therapy for patients with advanced-stage and unfavorable HL that responded to initial chemotherapy.[87,88] Neither trial showed an advantage for HDT/ASCR over conventional chemotherapy for patients with unfavorable and advanced HL experiencing complete or partial remission after an initial course of doxorubicin-based chemotherapy. Instead,

additional courses of the same conventional chemotherapy used as initial treatment produced equivalent or better outcomes than HDT/ASCR.

NCCN Recommendations—ABVD, Stanford V (selected patients with IPS <3), or escalated-dose BEACOPP (in selected patients aged <60 years with an IPS of ≥4) are included as options for primary treatment for patients with stage III–IV disease.[26,67,69,73]

ABVD is initially administered for 2 cycles followed by restaging with PET (see HODG-8; page 561). Patients with a Deauville score of 1 to 3 are treated with an additional 4 cycles (total of 6). Four additional cycles of ABVD (total of 6) followed by restaging are recommended for patients with a Deauville score of 4 or 5. Several ongoing studies have reported that early intensification to escalated BEACOPP in patients with a positive interim PET scan (based on the 5-PS) after 2 cycles of ABVD is associated with favorable outcomes.[23,89,90] Based on these findings, the guidelines recommend consideration of escalated BEACOPP (4 cycles) as an alternative option for patients with a Deauville score of 4 or 5 after 2 cycles of ABVD.

Consistent with the results of the E2496 study, observation or ISRT to initially bulky or selected PET-positive sites are included as options for patients with a Deauville score of 1 to 3 after 6 cycles of ABVD.[91] Biopsy is recommended for all patients with a Deauville score of 4 to 5 after 6 cycles of ABVD. Observation or ISRT to the mediastinum (if bulky mediastinal disease was initially present) are included as options for patients with negative biopsy results. Patients with positive biopsy results should be managed as described for refractory disease. Alternatively, ISRT to PET-positive sites could be considered for patients with a Deauville score of 4.

Stanford V is administered for 12 weeks (3 cycles) followed by restaging after chemotherapy (see HODG-9; page 562). ISRT (30–36 Gy; within 2–3 weeks after completion of chemotherapy) to initial sites greater than 5 cm and involved spleen is recommended for patients with a Deauville score of 1 to 4 and for those with a Deauville score of 5 with negative biopsy results.[92,93] Patients with positive biopsy results should be managed as described for refractory disease.

Escalated-dose BEACOPP is administered for 6 cycles followed by restaging with PET. No further treatment is necessary for patients with a Deauville score of 1 or 2 (see HODG-10; page 562). Based on the final results of the HD12 and HD15 trials, ISRT to residual PET-positive sites greater than 2.5 cm is recommended for patients with a Deauville score of 3 or 4 after 6 cycles of BEACOPP.[29,94] Biopsy is recommended for all patients with a Deauville score of 5 after 6 cycles of BEACOPP. Observation or ISRT to the initially bulky or PET-positive sites are included as options for patients with negative biopsy results. Patients with positive biopsy results should be managed as described for refractory disease.

The feasibility of deescalation of therapy to ABVD in patients with advanced-stage disease (IPS ≥3) who achieved a complete remission after 2 cycles of escalated BEACOPP has been demonstrated in studies conducted by the Israeli Study Group.[95] Interim restaging with PET

after 2 cycles of escalated BEACOPP with a possible deescalation of therapy to 4 cycles of ABVD may be considered in patients with negative interim PET results.

Follow-up After Completion of Treatment

The panel overwhelmingly agrees that, given the long-term risks of the therapies for HL, patients should undergo follow-up with an oncologist who is aware of these risks and complications, especially during the first 5 years after treatment to detect recurrence and then annually because of the risk for late complications, including secondary cancers and cardiovascular disease (see HODG-12; page 563).

The follow-up schedule should be individualized, depending on clinical circumstances, such as patient's age, stage of disease, and initial treatment modality. Recommendations included in the guidelines are based largely on the clinical practices at NCCN Member Institutions and are not supported by high-level evidence, because very few data are available on the follow-up and monitoring of late effects in patients with HL after completion of treatment.[96]

Refractory or Relapsed Disease

Two randomized phase III studies have showed significant improvement in EFS and PFS and FFTF (with no difference in OS) for patients with relapsed or refractory HL who underwent HDT/ASCR compared with conventional chemotherapy alone.[97,98] HDT/ ASCR is the best option for patients with HL that is not cured with primary treatment, even though it does not improve OS.

Several studies have shown the importance of cytoreduction with second-line chemotherapy before HDT/ASCR.[91–93,99–106] Bendamustine, lenalidomide, and everolimus have also shown activity in patients with relapsed or refractory HL.[94,107–108] However, none of these regimens has been studied in randomized trials. Second-line RT may be effective in patients who have a good performance status with limited-stage late relapses and no B symptoms.[102,109]

Brentuximab vedotin, a CD30-directed antibody drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas.[110] In a pivotal phase II multicenter study of 102 patients with relapsed or refractory HL after HDT/ASCR, brentuximab vedotin induced objective responses and complete remissions in 75% and 34% of patients, respectively, with a median follow-up of greater than 1.5 years. The median PFS for all patients and the median duration of response for those in complete remission were 5.6 months and 20.5 months, respectively.[111] Brentuximab vedotin is approved for the treatment of patients with HL after failure of HDT/ASCR, or at least 2 prior chemotherapy regimens in patients who are not candidates for HDT/ASCR. The 3-year follow-up data confirmed durable remissions in patients with disease responding to brentuximab vedotin.[112] After a median follow-up of approximately 3 years, the estimated median OS and PFS were 40.5 months and 9.3 months. In patients who achieved a complete remission on brentuximab vedotin, the estimated 3-year OS and PFS rates were 73% and 58%, respectively.[112]

The efficacy of brentuximab vedotin in patients with relapsed or refractory HL (before HDT/ASCR) was also confirmed in a recent prospective phase II study (n=36).[113] The best ORR was 69% (33% complete remission). The ORR was 75% for primary refractory disease and 66% for relapsed disease. Among 30 patients evaluable for HDT/ASCR, 27 (90%) successfully proceeded to HDT/ASCR.

NCCN Recommendations for Refractory Disease

Individualized treatment is recommended, because no data are available to support a superior outcome with any of the treatment modalities (see HODG-13; page 564).

Histologic confirmation with biopsy is recommended before initiating treatment. Conventional-dose second-line systemic therapy may precede HDT/ASCR. ISRT is recommended when the sites of relapse have not been previously irradiated. In radiation-naïve patients, total lymphoid irradiation may be an appropriate component of HDT/ASCR.[114] Everolimus and brentuximab vedotin are included as options for second-line systemic therapy for patients with relapsed or refractory CHL.[108,113] Bendamustine and lenalidomide are included as options for third-line therapy for patients with relapsed or refractory CHL.[94,107]

Second-line systemic therapy followed by response assessment with PET is recommended for all patients. Patients with a Deauville score of 1 to 3 should be treated with HDT/ASCR with or without ISRT or observation with or without ISRT, if HDT/ ASCR is contraindicated. Additional second-line therapy (ISRT or systemic therapy with or without ISRT) is recommended for patients with a Deauville score of 4 or 5. Alternatively, those with a Deauville score of 4 can be treated with HDT/ASCR with or without ISRT. Among patients with relapsed or refractory disease, some studies have suggested that patients who experienced complete remission with second-line therapy before HDT/ASCR or those with chemosensitive disease to second-line chemotherapy have improved outcomes after HDT/ASCR compared with those with resistant disease.[115,116]

The use of brentuximab vedotin as consolidation therapy after HDT/ASCR was evaluated in the AETHERA trial. In this trial, 329 patients who were at high risk of progression (patients with disease refractory to frontline therapy, relapsed disease less than 12 months after frontline therapy, and relapsed disease 12 or more months after frontline therapy with extranodal disease) were randomized (after HDT/ASCR) to brentuximab vedotin (n=165) or placebo (n=164).[117] Patients were required to have experienced a complete remission, partial remission, or stable disease with second-line therapy before ASCT. The interim analysis (after a median follow-up of 30 months) showed that early consolidation with brentuximab vedotin after HDT/ASCR was associated with improved PFS and the survival benefit was demonstrated across all risk groups. The median PFS was 42.9 months in the brentuximab vedotin group and 24.1 months in the placebo group. The estimated 2-year PFS rates were 65% and 45%, respectively, for the brentuximab vedotin and placebo arms (P=.0013). At the time of this interim analysis, no statistically significant difference in OS was seen between the groups (hazard ratio, 1.15; P=.6204). Brentuximab vedotin was also well tolerated. Peripheral sensory neuropathy (36%), upper respiratory tract infection (25%), neutropenia (24%), and fatigue (21%) were the most common adverse events.

Based on the results of this study, the panel has included maintenance therapy with brentuximab vedotin (for 1 year) after HDT/ASCR for patients with primary refractory disease or for those who experience disease relapse less than 12 months after primary treatment. However, the value of this approach in patients who have received prior treatment with brentuximab vedotin is not known.

NCCN Recommendations for Relapsed Disease

Although second-line systemic therapy is an appropriate treatment for any patient with relapsed disease, regardless of the length of initial remission,[89] some studies have also suggested that it may not be essential before proceeding to HDT/ASCR for patients with minimal residual disease at relapse.[90] In selected patients with long disease-free intervals and other favorable features, the selection of second-line therapy should be individualized (see HODG-14; page 564).

Suspected relapse should be confirmed with biopsy. Observation is appropriate if biopsy is negative. Restaging is recommended for patients with positive biopsy results. Second-line systemic therapy with or without ISRT or HDT/ASCR is the preferred treatment option for patients with stage IA to IIA disease who were initially treated with chemotherapy alone and experienced failure at the initial sites. RT alone may be appropriate for selected patients. All other patients experiencing disease relapse after initial treatment with chemotherapy or combined modality therapy should be treated with second-line systemic therapy.

Restaging after completion of treatment is recommended for all patients. Additional treatment options (based on the score on interim PET scan) are as described for patients with refractory disease.

Summary

HL is now curable in most patients because of the introduction of more-effective and less-toxic regimens. However, survivors may experience late treatment-related side effects. For this reason, long-term follow-up by an oncologist is essential after completion of treatment. Counseling about issues of survivorship and careful monitoring for late treatment-related side effects should be an integral part of follow-up. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.