NCCN Guidelines® Insights

Hodgkin Lymphoma, Version 2.2012

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Hodgkin Lymphoma (HL) include the clinical management of classical HL and lymphocyte-predominant HL (LPHL). Major changes have been incorporated into these guidelines since their inception. In the 2012 NCCN Guidelines for HL, PET scans are not recommended for interim restaging of patients with stage I to II favorable disease. After reevaluating the available evidence on the use of interim PET imaging, the panel recommends the use of diagnostic CT scan of involved sites for interim restaging after completion of chemotherapy for this group of patients. Maintenance rituximab for 2 years is included as an option for patients with stage IB to IIB or stage III to IV LPHL treated with rituximab alone in the first-line setting. Brentuximab vedotin is included as an option for patients with progressive disease or relapsed disease after second-line chemotherapy or high-dose therapy with autologous stem cell rescue. (*JNCCN* 2012;10:589–597)

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Disclosures for the NCCN Hodgkin Lymphoma Panel

Individual disclosures of potential conflicts of interest for the NCCN Hodgkin Lymphoma Panel members can be found online at NCCN.org.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the Panel's discussion, including the literature reviewed.

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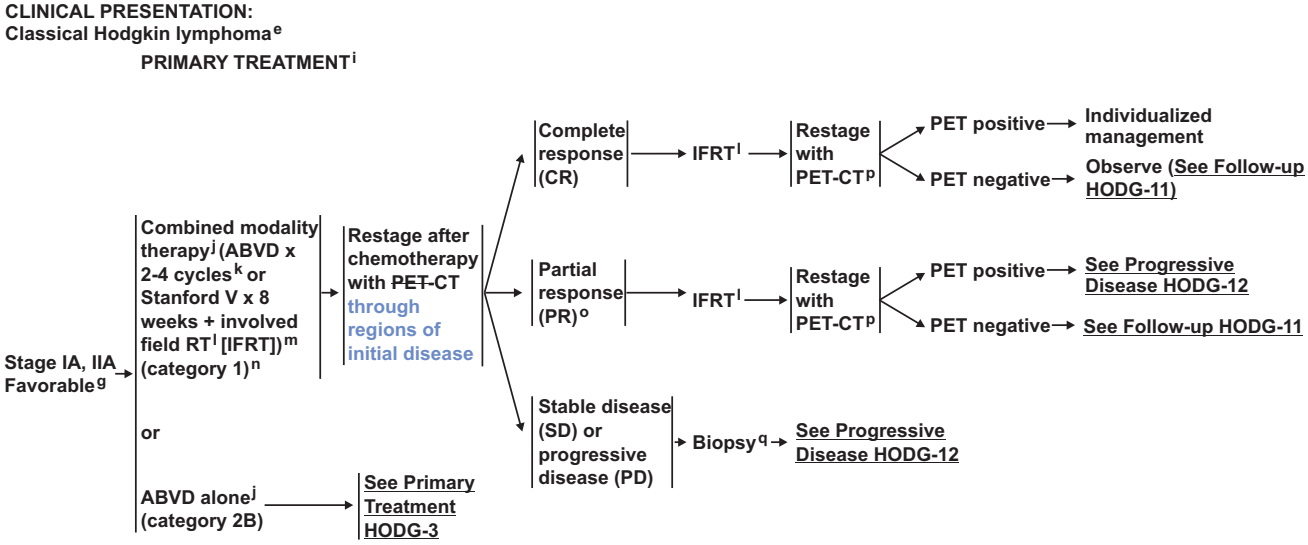
Hodgkin Lymphoma, Version 1.2012



[e] Classical Hodgkin lymphoma (HL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL) and lymphocyte-rich (LRHL).
[g] NCCN Unfavorable factors for stage I-II disease include bulky mediastinal or > 10 cm disease, B symptoms, ESR >50, >3 sites of disease (see Unfavorable Factors HODG-A).
[i] Individualized treatment may be necessary for older patients and patients with concomitant disease.
[j] See Principles of Systemic Therapy (HODG-B).
[k] 4 cycles of ABVD unless patient fulfills strict criteria of the GHSG with only 2 sites of disease and no extralymphatic lesions in which case 2 cycles is sufficient.
[l] See Principles of Radiation Therapy (HODG-C).
[m] Patients with elevated ESR or > 3 sites of disease may be managed with Stanford V per this algorithm.
[n] Depending upon co-morbidities, subtotal lymphoid irradiation (category 1) or mantle alone may be considered for patients not able to tolerate chemotherapy.
[o] Recommend ABVD x 4 cycles (total) before proceeding to IFRT or biopsy.
[p] An integrated PET-CT or a PET with a diagnostic CT is recommended.
[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.

HODG-2

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.

Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving the lymphatic system. Clinical management of patients with HL involves initial treatment with chemotherapy, combined modality therapy, or radiation therapy (RT) alone (for patients with lymphocyte-predominant HL [LPHL]), followed by restaging at the completion of therapy to assess treatment response. PET imaging and, more recently, integrated PET and CT (PET/CT, hereafter referred to as PET) is increasingly being used to assess treatment response during therapy, although the value of interim PET scans has not yet been established.[1] The introduction of more-effective and less-toxic front-line treatment options has significantly improved the prognosis of patients with HL. However, complete remission after initial therapy is not achieved in approximately 20% to 30% of patients with stage III to IV HL, eventually leading to disease progression.[2] In recent clinical trials, targeted

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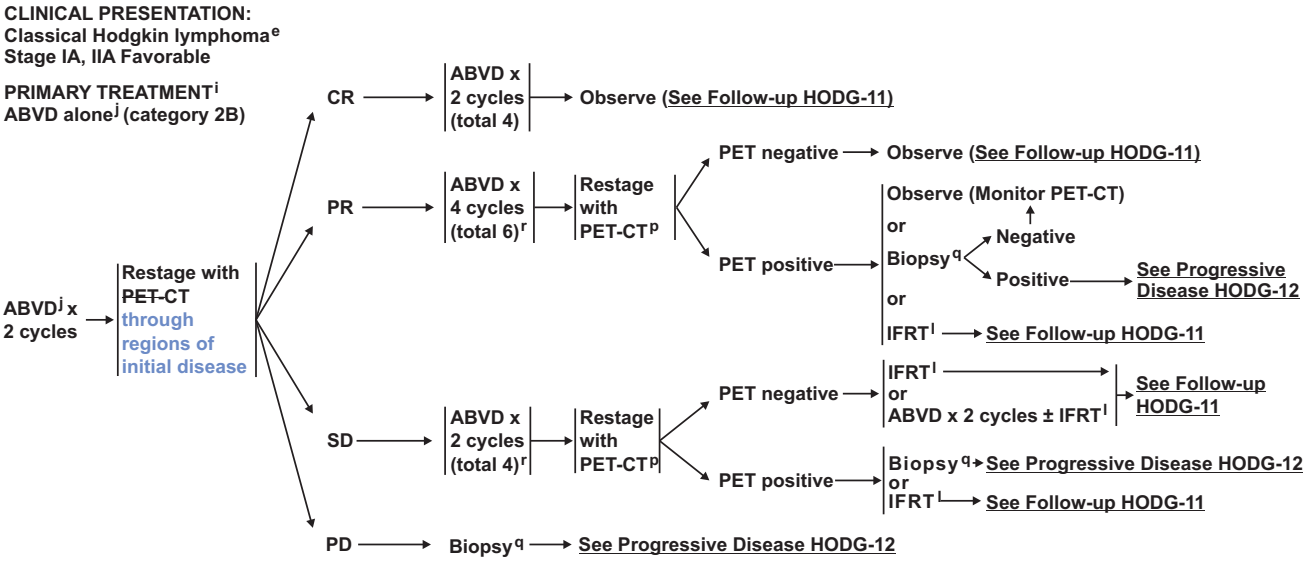

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[q]Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[r]Consider PFTs after 4 cycles of ABVD.

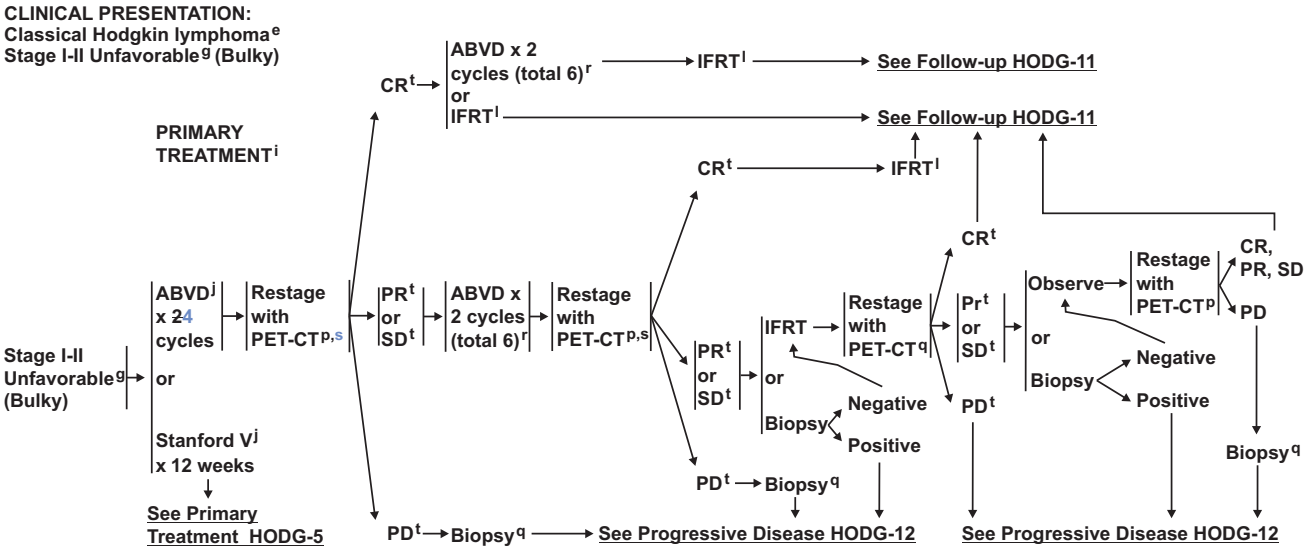
HODG-3

therapies with antibody drug conjugates (ADC) and monoclonal antibodies have shown promising results for patients with relapsed or progressive disease.[3,4] The following sections of these NCCN Guidelines Insights include the major discussion points from the 2011 Hodgkin lymphoma panel meeting.

Role of Interim PET Imaging in Classical HL

Early-Stage Disease

Available evidence, primarily from retrospective studies, suggests that interim PET imaging is not of prognostic significance in patients with early-stage disease. Hutchings et al.[5] reported that 5 of 7 (71%) patients with stage I to II disease who had a positive interim PET scan remained in remission at a median follow-up of 3 years, whereas all patients with advanced disease (stage III–IV) with a positive PET scan had experienced relapse within 2 years. More recent reports have confirmed these findings. In a study in which most patients had stage I to IIA disease (43 of 73), Sher et al.[6] reported that 65% of patients (13 of 20) with an interim positive PET scan after 2 to 3 cycles of chemotherapy had negative scans at the completion of chemotherapy; the actuarial 2-year failure-free survival was 92% compared with 96% for patients with negative PET scans during and after completion of chemotherapy. Barnes et al.[7] also showed that interim PET imaging did not predict outcome in patients with nonbulky stage I to II disease. The 4-year progression-free survival (PFS) rate was 91% for those with a negative interim PET scan and 87% for those with a positive interim scan ($P = .57$). In a recent prospective study, Straus et al.[8] reported that although both interim and end-of-treatment PET imaging was predictive of outcome in patients with stage I to II nonbulky disease treated with doxorubicin, vinblastine, and gemcitabine (AVG), the difference in the 2-year



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[i]Individualized treatment may be necessary for older patients and patients with concomitant disease.
[j]See Principles of Systemic Therapy (HODG-B).
[l]See Principles of Radiation Therapy (HODG-C).
[p]An integrated PET-CT or a PET with a diagnostic CT is recommended.
[q]Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[r]Consider PFTs after 4 cycles of ABVD.
[s]The value of interim PET imaging ~~scan after 2-4 cycles~~ is unclear ~~but may have a role in management and prognosis~~ for many clinical scenarios. All measures of response should be considered in the context of management decisions.
[t]See Revised Response Criteria for Lymphoma (HODG-D).

HODG-4

PFS rate was greater among patients with positive and negative PET scans after 6 cycles of AVG chemotherapy (27% and 89%, respectively) than after 2 cycles (50% and 90%, respectively).

Advanced-Stage Disease

Early interim PET imaging after chemotherapy has been shown to be a sensitive prognostic indicator of treatment outcome in patients with advanced disease (stage II disease with unfavorable risk factors or stage III–IV disease).[9] In 2 prospective studies, PET imaging after 2 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy was a strong and independent predictor of PFS in patients with advanced-stage disease.[10,11] In a combined report from these 2 prospective studies (190 patients with stage IIB–IVB; 70 patients with stage IIA with adverse prognostic factors), the 2-year PFS rate was significantly better for patients with a negative PET scan after 2 cycles of ABVD than those with a positive PET (95% vs. 13%; $P < .0001$).[12] Cerci et al.[13] reported similar findings in a recent prospective study that evaluated the prognostic value of PET imaging after 2 cycles of ABVD in patients with stage II to IV disease (102 patients; 35% had stage IV disease, 58% had bulky disease, and 63.5% had B symptoms); the 3-year event-free survival (EFS) rate was 53% for patients with a positive PET scan after 2 cycles and 90.5% for those with a negative scan ($P < .001$).

PET imaging after completion of 8 and 12 weeks of Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, and prednisone) or 4 cycles of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) chemotherapy were also predictive of freedom from progression (FFP) and PFS in patients with advanced-stage disease.[14,15]

NCCN Recommendations

The panel emphasizes that the value of interim PET imaging remains unclear, especially in patients with

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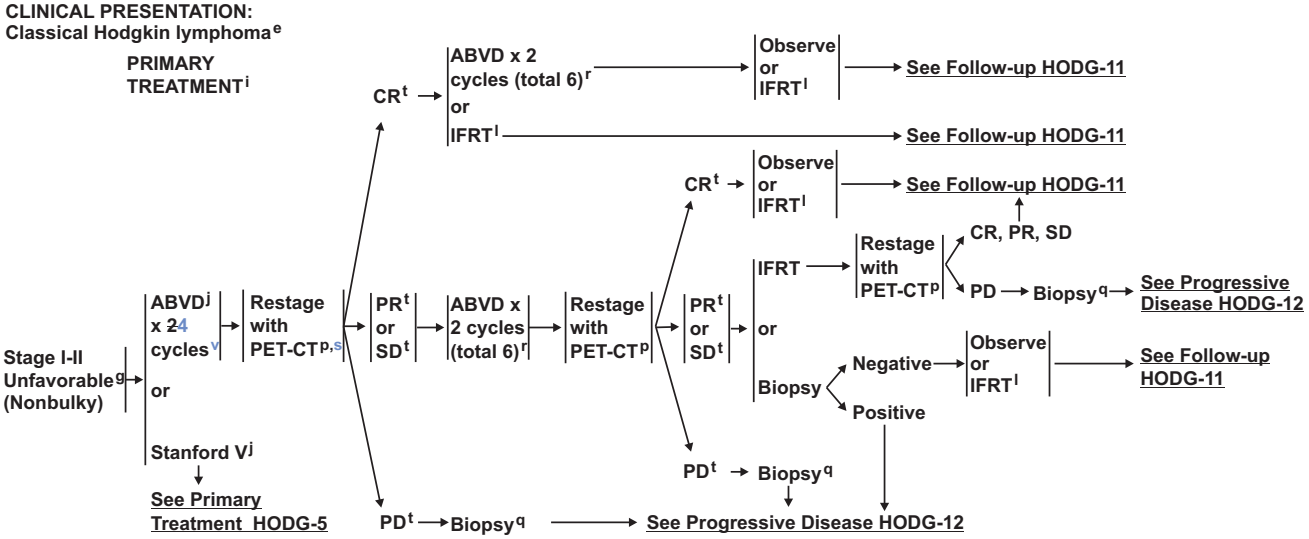

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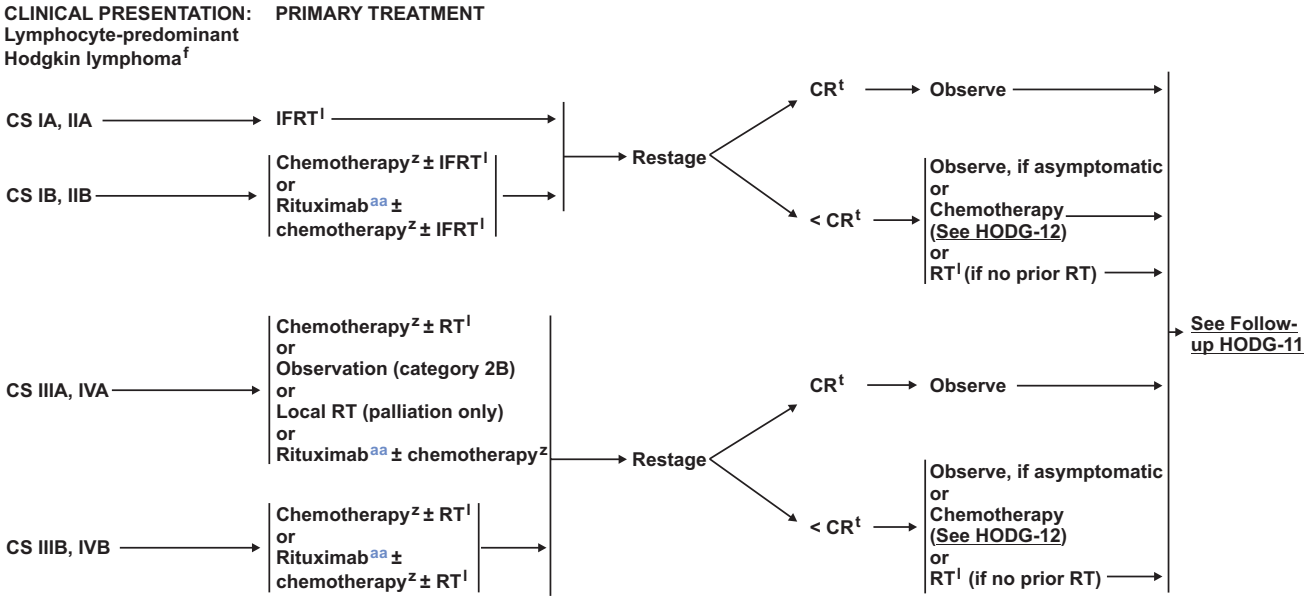
[t] See Revised Response Criteria for Lymphoma (HODG-D).
[v] If clinical circumstances warrant, initial PET-CT may be performed after just 2-3 cycles of ABVD.

HODG-6

stage I to II disease, and all measures of response should be considered in the context of management decisions. ***Stage IA to IIA (Favorable Disease):*** Patients with stage I to II disease with no risk factors have a favorable prognosis, with a cure rate of more than 90% with combined modality therapy (ABVD or Stanford V plus involved-field RT)[16–18] or chemotherapy with ABVD alone.[19,20] Available evidence also shows that patients with early-stage favorable disease with a positive PET scan after 2 to 3 cycles of chemotherapy have a better prognosis than those with advanced disease with a positive interim PET scan.[5–7] The panel consensus was that most patients (80%) undergoing combined modality therapy consistently have a negative PET scan after completion of chemotherapy, and complete the planned course of RT irrespective of whether the interim PET scan is positive or negative. Therefore, the panel believed that evidence was insufficient to recommend interim PET imaging for patients with stage I to II favorable disease. However, the panel agreed that interim imaging after completion of chemotherapy is essential in RT planning for patients receiving combined modality therapy. Interim imaging may also be useful to identify a subgroup of patients with early-stage disease that can be cured with 4 cycles of ABVD alone without the need for involved-field RT. In the National Cancer Institute of Canada (NCIC) study, patients assigned to ABVD alone were restaged with CT after 2 cycles; freedom from disease progression was superior in patients with stage I to II favorable nonbulky disease who, based on CT criteria, experienced a complete response (vs. those who did not) after 2 cycles of ABVD and who then received 2 more cycles of ABVD (4 total) without any RT.[19,20]

The recently updated NCCN Guidelines for Hodgkin Lymphoma recommend interim restaging of initial involved sites only with diagnostic CT after 2 to 4 cycles of ABVD for patients receiving combined modality therapy (see HODG-2) and after 2 cycles of ABVD for



[f]Lymphocyte-predominant has a different natural history and response to therapy than does classical Hodgkin lymphoma, especially stages I-II. For that reason, separate guidelines are presented for LPHL.
[l]See Principles of Radiation Therapy (HODG-C).
[t]See Revised Response Criteria for Lymphoma (HODG-D).
[z]See Principles of Systemic Therapy (HODG-B 2 of 2).
[aa]In some patients treated with rituximab alone, maintenance rituximab may be considered for 2 years.

HODG-10

patients receiving chemotherapy alone (see HODG-3), thereby reducing radiation exposure in patients with favorable disease with a good prognosis until the value of interim PET imaging is validated in prospective clinical trials (to view the most recent version of these guidelines, visit NCCN.org).

Stage I to II (Unfavorable, Bulky or Nonbulky Disease) and Stage III to IV Disease: Although the prognostic significance of interim PET imaging has been established in patients with advanced disease, the timing remains unclear. In one of the prospective studies, no significant difference was seen in the prognostic value of interim PET imaging after 2 versus 4 cycles of chemotherapy.[11] In a recent prospective study, interim PET imaging after 2 cycles of ABVD was highly predictive of treatment success in patients with stage I to II unfavorable disease and stage III to IV disease; the difference in 3-year EFS was significant for patients with stage III to IV disease ($P < .001$) and those with stage I to II disease ($P = .002$).[13]

Based on these findings, the recently updated guidelines recommend interim PET imaging after 4 cycles for patients with stage I to II (unfavorable, bulky, or nonbulky disease; see HODG-4 and HODG-6) and after completion of chemotherapy for patients with stage III to IV disease to assess response to therapy. The panel acknowledges that guiding therapy based on the results of interim PET imaging is considered investigational and is not recommended outside the context of a clinical trial.

Rituximab for the Management of Patients with LPHL

Involved-field RT alone is the preferred treatment for patients with stage IA or IIA disease, whereas chemotherapy with or without RT, observation, and palliative therapy are included as options for patients with more advanced disease. Because LPHL cells consistently express CD20 antigen, the efficacy of the anti-CD20 anti-

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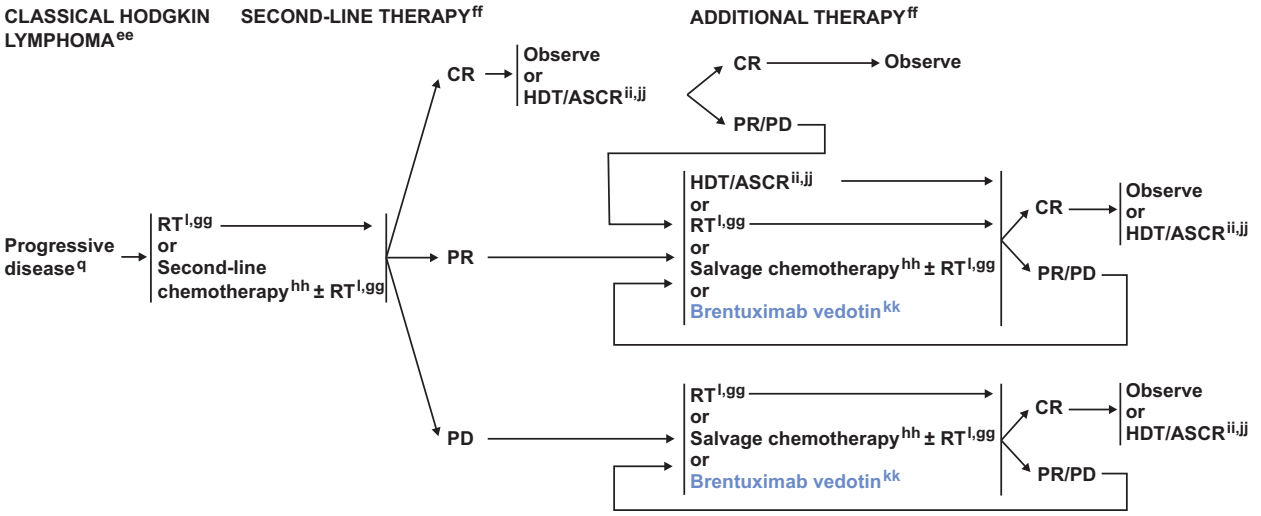

[l] See Principles of Radiation Therapy (HODG-C).
[q] Biopsy to confirm no change in histology. Clinical circumstances may warrant additional treatment even in face of negative biopsy.
[ee] Patients with LPHL may be managed according to the same algorithm; however, some patients with LPHL have a chronic indolent course that may not require aggressive re-treatment. These asymptomatic patients may be observed. At relapse, patient should be considered for re-biopsy because of risk for transformation.
[ff] There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.
[gg] Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.
[hh] See Principles of Second-Line Chemotherapy (HODG-E).
[ii] Radiation therapy recommended when sites have not been previously irradiated. In a radiation naive patient, TLI may be an appropriate component of HDT.
[jj] Allotransplant is an option in select patients as a category 3.
[kk] Brentuximab vedotin is a treatment option for patients who have failed HDT/ASCR or at least 2 prior multi-agent chemotherapy regimens.

HODG-12

body rituximab as a single agent or in combination with chemotherapy has been evaluated in clinical trials for patients with newly diagnosed and relapsed LPHL.[21–26]

In a prospective phase II trial conducted by the Stanford group, rituximab resulted in an overall response rate of 100% (41% complete response [CR], 54% partial response [PR], and 5% complete response uncertain [CRu]) in previously untreated or relapsed patients with stage I to IV LPHL; median FFP was 10 months.[21] The protocol was then modified to include extended treatment with rituximab for 2 years.[27] At a median follow-up of 60 months, the CR and CRu rates were 88% and 56%, respectively, for patients who underwent extended and limited rituximab treatment (P = .08).[27] The estimated FFP rates at 30 months were 88% and 52%, respectively. However, in a more recent report, rituximab maintenance for 2 years was not associated with a significant increase in median PFS compared with rituximab alone (67 and 50 months, respectively; P = .7; median follow-up, 8.8 years).[28]

NCCN Recommendations

Rituximab either as a single agent or in combination with chemotherapy (with or without RT) is included as first-line therapy for patients with stage IB or IIB or stage III to IV disease. Based on the earlier results of the study that showed higher response rates and more prolonged FFP in patients with newly diagnosed and relapsed LPHL treated with extended rituximab,[27] the panel has also included maintenance rituximab for 2 years as an option for patients treated with rituximab alone (see HODG-10).

Management of Patients With Relapsed or Progressive Disease

Second-line chemotherapy followed by high-dose therapy with autologous stem cell rescue (HDT/ASCR) is the standard treatment for patients with relapsed or refractory disease.[29,30] HDT/ASCR is only effective in 50% of patients and the prog-

nosis is poor for patients who experience relapse after HDT/ASCR, with a median survival of 25 months.[31]

With respect to HDT/ASCR, some studies have suggested that patients with a CR to second-line therapy before transplant or those with chemosensitive disease have improved outcomes after HDT/ASCR compared with those with resistant disease.[32,33] Moskowitz et al.[32] reported that the EFS, PFS, and overall survival rates were significantly better for patients responding to second-line chemotherapy (60%, 62%, and 66%, respectively) compared with those who had a poor response (19%, 23%, and 17%, respectively; $P < .001$). More recently, Sirohi et al.[33] reported similar findings; the 5-year overall survival rates were 79%, 59%, and 17%, respectively, for patients who were in CR or PR or those with resistant disease at HDT/ASCR ($P < .0001$), and the 5-year PFS rates were 69%, 44%, and 14%, respectively ($P < .001$).[33]

Brentuximab vedotin, a CD30-directed ADC, has shown activity in patients with relapsed or refractory CD30-positive lymphomas.[3] In a pivotal phase II multicenter study of 102 patients with relapsed or refractory HL after HDT/ASCR, brentuximab vedotin induced objective and complete responses in 75% and 34% of patients, respectively, with a median follow-up of 9 months.[34] Based on the results of this study, the FDA approved brentuximab vedotin 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.

NCCN Recommendations

In the recently updated NCCN Guidelines, brentuximab vedotin is included as an option for patients with progressive or relapsed disease. The consensus of the panel was that patients who are refractory to second-line chemotherapy should not proceed to HDT/ASCR, and those with progressive or relapsed disease who are not chemosensitive after 2 second-line chemotherapy regimens should be given a trial of brentuximab vedotin before HDT/ASCR, even though they may be candidates for transplant. Therefore, the panel has included brentuximab vedotin as an option for patients with progressive disease after HDT/ASCR or at least 2 prior chemotherapy regimens for all patients regardless of their eligibility for HDT/ASCR (see HODG-12).

Summary

The management of HL continues to evolve. 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; counseling on issues of survivorship and careful monitoring for late treatment-related side effects after completion of treatment should be an integral part of follow-up. Consistent with NCCN philosophy, participation in clinical trials is always encouraged.

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