NCCN Guidelines® Insights

Hodgkin Lymphoma, Version 1.2018

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Clinical Practice Guidelines in Oncology for Hodgkin Lymphoma (HL) provide recommendations for the management of adult patients with HL. The NCCN Guidelines Panel meets at least annually to review comments from reviewers within the NCCN Member Institutions, examine relevant data, and reevaluate and update the recommendations. These NCCN Guidelines Insights summarize recent updates centered on treatment considerations for relapsed/refractory classic HL.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Hodgkin Lymphoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Hodgkin Lymphoma

Disclosure of Relevant Financial Relationships

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^pAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^qSee PET 5-Point Scale (Deauville Criteria) (HODG-D).

^qSee Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E).

^rStrongly consider radiation therapy for selected sites that have not been previously irradiated. In a radiation-naïve patient, TLI may be an appropriate component of HDT.

^{ss}Allotransplant is an option in select patients as a category 3 recommendation.

^{tt}Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.

^{uu}See Principles of Radiation Therapy (HODG-C).

^{vv}Subsequent systemic therapy options include second-line therapy options that were not previously used (See HODG-E).

^{ww}Patients with 2 or more of the following risk factors are considered high risk: Remission duration less than 1 year, extranodal involvement, PET+ response at time of transplant, B symptoms, and/or >1 salvage/subsequent therapy regimen.

^{xx}Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;385:1853-1862.

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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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. The WHO classification divides HL into 2 main types: classic HL and nodular lymphocyte-predominant HL.¹ In 2018, an estimated 8,500 cases of HL will be diagnosed in the United States, with approximately 1,050 cases resulting in death.² Overall, 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. In fact, cure rates for HL have increased so markedly that overriding treatment considerations often relate to the reduction of long-term toxicity. However, 10% to 20%³⁻⁶ of patients with favorable features and early-stage disease and up to 30%^{7,8} with advanced-stage disease experience relapse.

The standard treatment option for chemosensitive patients with relapsed or refractory (R/R) HL is high-dose chemotherapy followed by autologous stem cell rescue or transplant (HDT/ASCR). Two randomized phase III studies performed by the

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CLASSIC HODGKIN LYMPHOMA
SUSPECTED RELAPSESECOND-LINE THERAPY^{yy}

^pAn integrated PET/CT or a PET with a diagnostic CT is recommended.

^sISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).

^{qq}See Principles of Systemic Therapy for Relapsed or Refractory Disease (HODG-E).

^{rr}Strongly consider radiation therapy for selected sites that have not been previously irradiated. In a radiation-naïve patient, TLI may be an appropriate component of HDT.

^{ss}Allotransplant is an option in select patients as a category 3 recommendation.

^{tt}Conventional-dose chemotherapy may precede high-dose therapy. Timing of RT may vary.

^{vv}Subsequent therapy options include second-line therapy options that were not previously used. (See HODG-E).

^{yy}There are no data to support a superior outcome with any of the treatment modalities. Individualized treatment is recommended.

^{zz}For patients not considered suitable for more aggressive therapy, radiation therapy can be used alone as a second-line therapy and conventional involved-field or extended-field treatment is indicated.

^{aaa}For select patients with long disease-free interval and other favorable features, selection of chemotherapy should be individualized.

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HODG-16

British National Lymphoma Investigation⁹ and the German Hodgkin Study Group (GHSg)/European Society for Blood and Marrow Transplantation¹⁰ compared HDT/ASCR with conventional chemotherapy alone in patients with R/R HL after a full course of conventional chemotherapy, and results showed significant improvement in event-free survival (EFS), progression-free survival (PFS), and freedom from treatment failure (FFTF) (with no difference in overall survival [OS]). For patients with recurrence after HDT/ASCR, treatment options are limited and most therapeutic strategies have been largely palliative.¹¹ With the recent approval of 3 novel agents (brentuximab vedotin [BV], nivolumab, and pembrolizumab), outcomes for patients with R/R disease have improved substantially.^{12–18} Emerging studies investigating novel agents and diverse combinations of therapeutic agents have the potential to enhance the treatment landscape and further improve outcomes for patients with R/R HL.

The NCCN Clinical Practical Guidelines in Oncology (NCCN Guidelines) for HL provide recommendations on standard treatment approaches based on current evidence. The panel updates the guidelines annually, with additional interim updates as needed. These NCCN Guidelines Insights summarize treatment recommendations for R/R classic HL and highlight important updates with relevant supporting data.

Updates to the Treatment of R/R Classic HL

Second-Line and Subsequent Systemic Therapy

Several studies have shown the importance of cytoreduction with second-line chemotherapy before HDT/ASCR.^{19–28} Newer regimens, such as GVD (gemcitabine/vinorelbine/pegylated liposomal doxorubicin),²⁹ IGEV (ifosfamide/gemcitabine/vinorelbine),³⁰ and GCD (gemcitabine/carboplatin/dexamethasone),^{31,32} have also demonstrated efficacy in R/R HL. In addition, bendamustine, lenalidomide,

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE (1 OF 3)
Regimens**Second-Line Systemic Therapy Options (listed in alphabetical order):**

- Brentuximab vedotin (only for CHL)¹ alone or in combination with the second-line regimens below
- DHAP (dexamethasone, cisplatin, high-dose cytarabine)^{2,3}
- ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin)^{4,5,6}
- Gemcitabine/bendamustine/vinorelbine⁷
- GVD (gemcitabine, vinorelbine, liposomal doxorubicin)⁸
- ICE (ifosfamide, carboplatin, etoposide)^{9,10}
- IGEV (ifosfamide, gemcitabine, vinorelbine)¹¹

Subsequent Systemic Therapy Options* (only for CHL) (listed in alphabetical order):

- Bendamustine¹²
- C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) (category 2B)
- Everolimus¹³
- GCD (gemcitabine, carboplatin, dexamethasone)^{14,15}
- Lenalidomide¹⁶
- MINE (etoposide, ifosfamide, mesna, mitoxantrone)¹⁷
- Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)^{18,19}
- Nivolumab^{20,21} (for relapsed or refractory CHL following HDT/ASCR)
- Pembrolizumab²² (for relapsed or refractory CHL after ≥3 prior lines of therapy)

See Check Point Inhibitors (CPI) HODG-E 2 of 3

*Subsequent systemic therapy options include second-line therapy options that were not previously used.

See References (HODG-E 3 of 3)

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HODG-E
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and everolimus have shown activity in patients with R/R HL.^{33–35} In a phase II trial, bendamustine was well tolerated and highly active in heavily pretreated patients with R/R disease (including those with disease that failed to respond to HDT/ASCR), resulting in an overall response rate (ORR) of 56% among evaluable patients (34/36 patients enrolled).³³ The ORR by intent-to-treat analysis was 53% (including 33% complete responses [CRs] and 19% partial responses [PRs]), and the median response duration was 5 months. Lenalidomide and everolimus have also shown single-agent activity in a small cohort of patients with R/R HL, resulting in ORRs of 19% and 47%, respectively.^{34,35} In a recent phase II study, bendamustine in combination with gemcitabine and vinorelbine (BeGEV) was used as induction therapy before autologous stem cell transplantation (ASCT) in patients with R/R HL, resulting in an ORR of 83% (CR, 73%; PR, 10%).³⁶ In selected patients with long disease-free intervals and other favorable

features, the selection of second-line therapy should be individualized.

During the 2018 update, the NCCN panel made distinctions between regimens used as second-line and subsequent systemic therapy options, and the BeGEV regimen was added to the list of second-line systemic therapy options for R/R HL (HODG-E 1 of 3; page 249).

HDT/ASCR or Allogeneic Hematopoietic SCT

The goal of second-line therapy is to attain a PET-negative CR before HDT/ASCR,³⁷ because this marker of chemosensitivity is associated with improved outcomes compared with outcomes observed with resistant disease.^{38,39} Moskowitz et al³⁸ reported that EFS, PFS, and OS were significantly better for patients with disease responding to second-line chemotherapy (60%, 62%, and 66%, respectively) compared with those who experienced a poor response (19%, 23%, and 17%, respectively) ($P<.001$). Sirohi et al³⁹ reported similar findings: the 5-year OS rates in their study were 79%, 59%, and

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSED OR REFRACTORY DISEASE (2 OF 3)
CHECKPOINT INHIBITORS (CPI)

FDA Approved Indications:^{1,2}

- Nivolumab is indicated for the treatment of adult patients with CHL that has relapsed or progressed after:
 - Autologous HSCT and brentuximab vedotin; or
 - 3 or more lines of systemic therapy that includes autologous HSCT.
- Pembrolizumab is indicated for the treatment of adult and pediatric patients with refractory CHL, or those who have relapsed after 3 or more prior lines of therapy.

General guidelines for use:

- CPI are commonly recommended for:
 - Patients with refractory CHL who are transplant-ineligible based on comorbidity or failure of first salvage chemotherapy.
 - Any patient who has relapsed after autologous HSCT ± brentuximab vedotin.
- Post-allogeneic transplant, patients can receive either nivolumab or pembrolizumab. There are limited data regarding the use of CPI following allogeneic transplantation. Caution is advised due to increased risk of GVHD (graft-versus-host disease) and other immunological complications.
- Nivolumab has not been studied in pediatric patients; therefore, only pembrolizumab should be offered.

¹National Institutes of Health. Nivolumab package insert. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f570b9c4-6846-4de2-abfa-4d0a4ae4e394>. Accessed December 20, 2017.

²National Institutes of Health. Pembrolizumab package insert. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9333c79b-d487-4538-a9f0-71b91a02b287>. Accessed December 20, 2017.

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17%, respectively, for patients who were in CR, PR, or those with resistant disease at the time of HDT/ASCR ($P<.0001$), and the 5-year PFS rates were 69%, 44%, and 14%, respectively ($P<.001$).

Several investigators have developed prognostic models to predict outcomes in patients with R/R disease undergoing HDT/ASCR. Brice et al⁴⁰ used end-of-treatment to relapse interval (≤ 12 months) and extranodal disease at relapse as adverse prognostic factors to predict outcomes for 280 patients undergoing HDT/ASCR. PFS rates were 93%, 59%, and 43% for patients with 0, 1, or 2 of these risk factors, respectively. In a prospective study, Moskowitz et al²⁶ identified extranodal sites, complete remission duration of <1 year, primary refractory disease, and B symptoms as adverse prognostic factors associated with poor survival after HDT/ASCR. In patients with 0 or 1 factor, 5-year EFS and OS were 83% and 90%, respectively, which decreased to 10% and 25% if all factors were present. This prognostic model has been used for the risk-adapted augmentation of treatment for R/R

disease to improve EFS in poorer-risk patients.⁴¹ In a retrospective analysis of 422 patients with relapsed disease from the GHSG database, Josting et al⁴² identified time to relapse, clinical stage at relapse, and anemia at relapse as independent risk factors to develop a prognostic score that classified patients into 4 subgroups with significantly different freedom from second failure and OS. GEL/TAMO investigators identified bulky disease at diagnosis, a short duration of first complete remission (<1 year), detectable disease at transplant, and the presence of >1 extranodal site as adverse factors for OS.⁴³ Other groups have identified extent of prior chemotherapy,⁴⁴ short time from diagnosis to transplant,⁴⁵ and disease status at transplantation⁴⁶ as significant prognostic factors for OS and PFS. Pretransplant functional imaging status has also been identified as an independent predictor of outcome in patients with R/R HL.^{47–50}

Nonmyeloablative allogeneic transplant using posttransplant cyclophosphamide has excellent outcomes even in haploidentical patients with estimat-

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ed OS and PFS rates of 63% and 59%, respectively, at 3 years.⁵¹ During the 2018 update, the NCCN panel included autologous or allogeneic SCT as an option for patients with PET-positive refractory HL (Deauville 5) that is responsive to radiation therapy (RT) alone or to subsequent systemic therapy ($\pm$ RT) (see HODG-15; page 247).

Brentuximab Vedotin

BV, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with R/R CD30+ lymphomas.¹⁶ In a pivotal phase II multicenter study of 102 patients with R/R HL after HDT/ASCR, BV induced objective responses and complete remissions in 75% and 34% of patients, respectively, with a median follow-up of >1.5 years. Median PFS for all patients and the median duration of response for those in complete remission were 5.6 and 20.5 months, respectively.¹⁷ The 3-year follow-up data confirmed durable remissions in patients whose disease responded to BV.¹⁵ After a median follow-up of approximately 3 years, the estimated median OS and PFS were 40.5 and 9.3 months, respectively. In those who experienced a complete remission on BV, the estimated 3-year OS and PFS rates were 73% and 58%, respectively.¹⁵

Recent studies are investigating the utility of BV as second-line therapy for R/R HL, either sequentially or in combination with other regimens, prior to HDT/ASCR.^{11,52–56} A multicenter prospective phase II study examined the efficacy of BV in patients (n=37) with R/R HL (prior to HDT/ASCR), which resulted in an ORR of 68% (CR, 35%), and 33 patients (89%) successfully proceeded to HDT/ASCR.⁵² Other studies have combined BV with bendamustine, ICE (ifosfamide/carboplatin/etoposide), or ESHAP (etoposide/methylprednisolone/high-dose cytarabine/cisplatin), with preliminary data demonstrating PET-negative responses ranging from approximately 75% to 90%.^{11,53,54,56} During the 2018 guideline update, the NCCN panel included a recommendation that BV could be used alone or in combination with second-line systemic therapy options for R/R HL (HODG-E 1 of 3; page 249).

Use of BV as consolidation or maintenance therapy following HDT/ASCR was evaluated in the AETHERA trial.⁵⁷ In this trial, 329 patients who were at high risk of progression after HDT/ASCR (patients with disease refractory to frontline therapy, relapsed disease <12 months after frontline therapy, or extra-

nodal disease at the start of pretransplantation salvage chemotherapy) were randomized to BV (n=165) or placebo (n=164).⁵⁷ Patients were required to have obtained a complete remission, partial remission, or stable disease to second-line therapy prior to ASCT. After a median follow-up of 30 months (range, 0–50 months), primary analysis showed that early consolidation with BV after HDT/ASCR was associated with improved PFS, and the survival benefit was demonstrated across all risk groups. Median PFS was 42.9 months in the BV group and 24.1 months in the placebo group. The estimated 2-year PFS rates by independent review were 63% and 51%, respectively, for the BV and placebo arms ($P=.0013$). The benefit of BV on PFS in this context appeared to decrease in patients who were PET-negative before HDT/ASCR.⁵⁷

During the 2018 update, the panel clarified the patient subpopulation likely to gain maximal benefit from BV use as maintenance therapy for 1 year after HDT/ASCR (see HODG-15; page 247). These are patients with high risk of relapse with ≥ 2 of the following risk factors: remission duration of <1 year, extranodal involvement, PET-positive at transplant, B symptoms, and/or >1 salvage/subsequent therapy regimen (see HODG-15; page 247).

Programmed Death Receptor-1 Inhibitors

Blockade of the programmed death receptor-1 (PD-1), an immune checkpoint, has demonstrated activity in patients with R/R PD-1–positive lymphomas.^{12–14,18,37,58} In a phase I study of 23 patients with R/R HL pretreated with both HDT/ASCR and BV, treatment with nivolumab, a PD-1 inhibitor, induced an ORR of 87%, with a PFS rate of 86% at 24 weeks.¹² In a phase II study of 80 patients with R/R HL pretreated with both HDT/ASCR and BV, treatment with nivolumab induced an objective response in 53 of 80 patients (66.3%; 95% CI, 54.8–76.4), as determined by an independent radiologic review committee, at a median follow-up of 8.9 months.¹⁸ In a phase I study of 31 patients with R/R HL pretreated with BV, treatment with pembrolizumab, another PD-1 inhibitor, induced a complete remission rate of 16% (90% CI, 7%–31%) and a partial remission rate of 48% resulting in an ORR of 65% (90% CI, 48%–79%).¹³ In a phase II study of 210 patients with R/R HL, the efficacy of pembrolizumab was examined in 3 cohorts of patients with disease progression after (1) ASCT and subsequent BV, (2) salvage chemotherapy and BV (ineligible for ASCT due to

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chemoresistant disease), and (3) ASCT without BV¹⁴; the corresponding ORRs were 73.9%, 64.2%, and 70%, respectively.¹⁴ During the 2018 guideline update, the panel clarified and expanded on contexts for the use of the PD-1 inhibitors nivolumab and pembrolizumab as subsequent systemic therapy options for R/R classic HL (see HODG-E 1 and 2 of 3; pages 249 and 250, respectively). Emerging data are investigating the combination of BV and checkpoint inhibitors as an option for R/R HL prior to transplant.⁵⁹

Radiotherapy

Josting et al⁶⁰ from the GHSG reported on the effectiveness of second-line RT in a select subset of patients with R/R disease. The 5-year FFTR and OS rates were 28% and 51%, respectively. B symptoms and stage at time of disease progression or relapse were identified as significant prognostic factors for OS. Moskowitz et al²⁶ have demonstrated the efficacy and feasibility of second-line RT with chemotherapy in patients with R/R disease. At a median follow-up of 43 months, the response rate to the ICE regimen and involved-field RT was 88%, and the EFS rate for patients who underwent HDT/ASCR was 68%. Thus, RT may improve the chance of transitioning to HDT/ASCR in R/R disease. Alternately, second-line RT may be effective in patients with a good performance status with limited-stage late relapses and without B symptoms. It may be a very effective treatment for patients with initial favorable stage I–II disease who are treated with chemotherapy alone and experience relapse in initially involved sites. During the 2018 update, the NCCN panel revised the treatment algorithm for patients with relapsed HL with initial stage IA–IIA disease and no prior RT to include options for those who received either abbreviated chemotherapy without RT or a full course of chemotherapy (see HODG-16; page 248). A comprehensive review and recommendations for incorporation of RT into salvage treatment programs is provided by the International Lymphoma Radiation Oncology Group consensus guidelines.⁶¹

NCCN Recommendations for R/R Classic HL

Histologic confirmation with biopsy is recommended before initiating treatment for refractory disease. Second-line systemic therapy is recommended for all patients with refractory disease, followed by response assessment with PET. Patients with a Deauville score

of 1 to 3 should then be treated with HDT/ASCR with or without RT (category 1 recommendation), followed by observation or 1 year of BV maintenance therapy for patients with a high risk of relapse as defined by the AETHERA trial.⁵⁷ RT should be strongly considered for selected sites of relapse that have not been previously irradiated. If HDT/ASCR is contraindicated, observation with or without RT is recommended. For patients with a Deauville score of 4 or 5 after second-line systemic therapy, subsequent systemic therapy ($\pm$ RT) or RT alone is recommended, followed by repeat response assessment. Alternatively, those with a Deauville score of 4 can be treated with HDT/ASCR with or without RT, followed by observation or 1 year of BV maintenance therapy for patients with a high risk of relapse. If patients with a Deauville score of 5 are responsive to secondary therapy, autologous or allogeneic SCT is an option.

Suspected relapse at any point should be confirmed with a biopsy. Observation (with short-interval follow-up with PET/CT) is appropriate if biopsy is negative. Restaging is recommended for patients with positive biopsy. Second-line systemic therapy with RT or HDT/ASCR with or without RT are treatment options for patients with stage IA–IIA disease who were initially treated with chemotherapy alone and experienced failure at the initial sites. RT alone may be appropriate in highly selected patients who received abbreviated chemotherapy (3–4 cycles) without RT. 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 treatment completion is recommended for all patients. Subsequent treatment options (based on the score on interim PET scan) are described for patients with refractory disease (see HODG-E 1 of 3; page 249).

Summary

These NCCN Guidelines Insights highlight updates to the recommendations for the management of R/R classic HL in the 2018 version of the NCCN Guidelines for HL. Several factors need to be considered to guide effective management of R/R HL, including prognostic risk factors that modulate response to therapy, age, comorbidities, prior therapy, and eligibility for transplant. Although further cytoreduction and HDT/ASCR (with RT if not previously given) are often appropriate, occasional clinical circum-

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stances may warrant the use of RT or systemic therapy with or without RT. Individualized treatment is recommended, because no data support a superior outcome with any of the treatment modalities. The

challenge of treating patients with chemorefractory disease may be improved as more evidence emerges regarding the use of novel agents, alone or in combination, prior to transplant.

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Posttest Questions

1. Based on the AETHERA trial, patients with refractory HL and a high risk of relapse are more likely to benefit from consolidation or maintenance therapy with BV after HDT/ASCR. Which of the following risk factors is not associated with a high risk of disease progression?
 - a. Remission duration <1 year
 - b. B symptoms
 - c. Detectable extranodal disease prior to transplant
 - d. PET-negative at time of transplant
2. In the NCCN Guidelines for HL, which of the following

may be considered as second-line chemotherapy options for patients with relapsed classic HL?

- a. BV and ICE
- b. Nivolumab and cisplatin/docetaxel
- c. CHOP + rituximab
- d. A and B

3. True or False: The PD-1 inhibitor nivolumab is a treatment option for adult patients with classic HL that has relapsed or progressed after at least 3 prior lines of systemic therapy.