Hodgkin's Lymphoma: Saudi Lymphoma Group's Clinical Practice Guidelines for Diagnosis, Management and Follow-up

Hani Alhashmi[1], Magdy Kandil[2,3], Ayman Alhejazi[4], Ibraheem Motabi[5], Ahmed Sagheir[6], Musa Alzahrani[7], Reyad Dada[8,9], Mubarak Al-Mansour[10,11]

[1]Adult Hematology and Stem Cell Transplantation Department, King Fahad Specialist Hospital, Dammam, [2]Oncology Department, Prince Sultan Military Medical City, [4]Department of Oncology, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Central Region, [5]Department of Adult Hematology and BMT, Comprehensive Cancer Center, King Fahad Medical City, [7]Department of Medicine, College of Medicine, King Saud University, [9]College of Medicine, Alfaisal University, Riyadh, [6]Oncology Institute, John Hopkins Aramco Healthcare, Dhahran, [8]Department of Oncology, King Faisal Specialist Hospital and Research Centre, [10]College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, [11]Adult Medical Oncology, Princess Noorah Oncology Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Western Region, Jeddah, Saudi Arabia, [3]Clinical Oncology Department, Cairo University, Giza, Egypt

Address for correspondence:
Dr. Mubarak Al-Mansour, College of Medicine, Adult Medical Oncology, Princess Noorah Oncology Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Western Region, PO Box 9515, Jeddah 21423, Kingdom of Saudi Arabia.
E-mail: drmubarak55@hotmail.com

Received: 24-03-2019 **Revised:** 15-05-2019 **Accepted:** 24-07-2019 **Published:** 28-08-2019

INTRODUCTION

Hodgkin's lymphoma (HL) is a rare B-cell malignancy involving lymph nodes and the lymphatic system. It accounts for 3.6% of all cancers in Saudi Arabia, with 436 new cases in 2015. In HL, there is a slight male predominance, and it is the seventh and eight most common cancer among Saudi males and females, respectively. In 2015, the age-standardized rate was 2.6/100,000 for males and 1.7/100,000 for females. In addition, the median age at diagnosis was 26 years in both genders (range among males: 3–84 years; females: 4–89 years).[1]

METHODS

A committee comprising experts in hematology and medical oncology was established under the supervision of the Saudi Lymphoma Group and in collaboration with the Saudi Oncology Society. For collecting evidence, a literature search was carried out with relevant keywords using online database search engines such as PubMed/Medline, Web of Science and Scopus. In addition, expert opinion was considered when necessary. The levels of evidence used in developing this guideline were as follows:

- Evidence level (EL)-1 (highest), evidence from Phase III randomized trials or meta-analyses
- EL-2 (intermediate), evidence from well-designed Phase II trials or Phase III trials with limitations
- EL-3 (low), evidence from retrospective or observational studies/reports and/or expert opinion.

This easy-to-follow grading system is convenient for readers to understand and allows an accurate assessment of the guideline's applicability in individual patients.[2]

1. DIAGNOSIS AND WORK-UP

1.1. The diagnostic work up for HL patients has evolved since the introduction of positron emission tomography-computed tomography (PET/CT) scanning. In patients undergoing PET/CT evaluation, a bone marrow biopsy

Access this article online

Quick Response Code:

Website: www.sjmms.net

DOI: 10.4103/sjmms.sjmms_96_19

How to cite this article: Alhashmi H, Kandil M, Alhejazi A, Motabi I, Sagheir A, Alzahrani M, *et al*. Hodgkin's lymphoma: Saudi Lymphoma Group's Clinical Practice Guidelines for diagnosis, management and follow-up. Saudi J Med Med Sci 2019;7:195-201.

is not indicated. However, if PET/CT is not available, bone marrow biopsy should be carried out in patients with advanced stage disease, B-symptoms and/or abnormal complete blood count (CBC) (EL-1)[3-5]

1.2. A diagnostic assessment based solely on fine needle aspiration is insufficient (EL-3)[6-8]

1.3. Before initiating treatment, cardiac and pulmonary function tests should be carried out to identify patients at increased risk of acute or chronic complications. In addition, young patients should be offered reproductive counseling before the treatment is initiated, as chemo-and radiotherapy can permanently impair fertility

1.4. Summary of the diagnostic work-up (EL-1).[3-5,9,10]

- 1.4.1. Evaluations should include complete history and physical examination
- 1.4.2. Excisional biopsy is the optimal method for diagnosis
- 1.4.3. Laboratory evaluations of all patients should comprise CBC, renal and liver profile, albumin, as well as routine blood chemistry including lactate dehydrogenase and erythrocyte sedimentation rate
- 1.4.4. Bone marrow biopsy is recommended if PET is not available for patients with advanced stage disease, B-symptoms and/or abnormal CBC
- 1.4.5. Pregnancy test should be done for women of childbearing age
- 1.4.6. Patients should be screened for hepatitis B, hepatitis C and human immunodeficiency viruses
- 1.4.7. Thyroid-stimulating hormone (TSH) test should be carried out if radiation is planned.
- 1.4.8. PET/CT is the preferred imaging modality
- 1.4.9. CT scan of neck, chest, abdomen and pelvis (CAP) should be performed in all cases
- 1.4.10 Cardiac function should be assessed by multigated acquisition scan or 2D echocardiography
- 1.4.11. Pulmonary function test should be done in all cases.

1.5. Several prognostication models have been developed in the past decades. One of these is the International Prognostic Score (IPS), which is defined as the number of adverse prognostic factors present at diagnosis, with the score ranging from 0 to 7 IPS helps determine the clinical management and predict prognosis for Stages III and IV patients (EL-1).[11] Patients with a score of 0 and ≥5 have a median 5-year survival of 89% and 56%, respectively.

- 1.5.1. International Prognostic Score for Hodgkin Lymphoma (Stages III and IV)
  - 1.5.1.1 Serum albumin <40 g/L
  - 1.5.1.2 Hemoglobin <105 g/L
  - 1.5.1.3. Male gender
  - 1.5.1.4. Stage IV disease
  - 1.5.1.5. Age >45 years
  - 1.5.1.6 White blood cell count ≥15,000/mm^3
  - 1.5.1.7 Lymphocyte count <600/mm^3 or <8% of white cell count.

2. PATHOLOGICAL DIAGNOSIS

2.1. Excisional biopsy is the preferred method for diagnosis, provided adequate material is obtainable for fresh frozen and formalin-fixed samples. Diagnosis should be in accordance with the World Health Organization classification

2.2. For confirming the diagnosis of classic HL, it is recommended that the immunohistochemistry panel should include CD3, CD15, CD20, CD30, CD45, CD79a and PAX5

2.3. Classic HL and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) have significantly different malignant cell phenotypes

2.4. In classic HL, malignant cells are positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45, whereas in NLPHL, malignant cells are positive for CD20 and CD45, but negative for CD15 and CD30 (EL-1).[12]

3. STAGING

3.1. There are two practical approaches for staging HL: The North American (United States and Canada) and European (European Organisation for Research and Treatment of Cancer, Germany) approach. We recommend the North American approach, where patients can be classified to limited or advanced disease based on stage, presence/absence of B-symptoms and presence/absence of bulky disease (EL-3)[9-11]

3.2. Stage: Stages I and II versus Stage III and IV according to the Ann Arbor staging system

3.3. B-symptoms is defined as recurrent unexplained fever of >38°C, recurrent night sweats or unexplained weight loss of ≥10% in the past 6 months

3.4. Bulky disease is defined as having a tumor of diameter ≥10 cm on CT scan.

4. MANAGEMENT OF CLASSICAL HODGKIN'S LYMPHOMA

4.1. Limited Stage I and II (non-bulky and no B-symptoms)

4.1.1. The preferred treatment is a combined therapy of two cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) plus 30 Gy of involved-field radiation therapy (ISRT) (EL-1)[13-18]

4.1.2. ABVD alone is also an effective treatment modality, especially among younger patients (i.e., <60 years old) who achieve complete remission after two cycles, according to the interim PET/CT (Deauville score of 1–3). In these patients, there should only be subsequent one or two cycles of ABVD (i.e., a total of three to four cycles of ABVD) to avoid the long-term risks of radiotherapy (EL-1)[15,19-24]

4.1.3. However, if interim PET/CT is positive for residual disease (Deauville score of 4 or 5), it is recommended to complete the planned two cycles of ABVD plus ISRT. If end-of-therapy PET/CT is positive for residual disease, it is recommended to re-biopsy, and if positive, proceed to salvage therapy (EL-1).[15,19,25-27]

4.2. Advanced stage (Stages III or IV, bulky and/or B symptoms)

4.2.1. ABVD is recommended as the preferred first-line therapy. Another option is brentuximab plus adriamycin, vinblastine and dacarbazine (AVD) in selected patients if IPS >4, bleomycin contraindicated, no known neuropathy (EL-1).[13,26-36]

4.2.1.1. Two cycles of ABVD should be followed by an interim PET/CT (EL-1)[13]

4.2.1.2. Patients with a negative interim PET/CT (Deauville score of 1–3) should be treated with an additional four cycles of AVD (i.e. a total of six cycles) followed by observation (EL-1)[26]

4.2.1.3. In patients with a positive interim PET/CT (Deauville score of 4–5):

4.1.2.1.3.1. Treat with an additional four cycles of ABVD (i.e. a total of 6 cycles)[26]

4.1.2.1.3.2. An alternative approach is treating with four cycles of escalated BEACOPP with or without ISRT (EL-1).[28,30,31]

4.2.1.4. An end-of-therapy PET/CT should be carried out 6–8 weeks after completion of chemotherapy and 8–12 weeks after completion of radiotherapy. For single-site residual disease, the following is recommended (EL-1):[26]

4.2.1.4.1. If PET/CT is negative, observe.

4.2.1.4.2. If PET/CT is positive, a biopsy is recommended if accessible, otherwise ISRT is indicated.

4.2.1.4.3. If the biopsy is negative, observe with or without ISRT

4.2.1.4.4. Patients with a positive biopsy can be managed either with ISRT or as a refractory disease (described in Section 4.3 below).

4.2.1.5. If PET/CT is not available, then a CT scan can be utilized to assess response after three to four cycles. In clinically responding patients, proceed to completing the six cycles of ABVD. However, if there is evidence of disease progression, then consider it as a refractory disease, and proceed with salvage chemotherapy and autologous stem cell transplantation (ASCT)(EL-3).

4.3. Refractory/Relapsed disease

Most patients with HL achieve complete remission and long-term disease control with standard management approach. However, relapse may occur in about 10% of patients with limited HL and in 15%–30% of patients with advanced HL. Approximately 10%–15% of patients may have refractory disease that either does not respond to standard therapy or progresses after an initial partial response (EL-1).[13,18,20,23,35]

4.3.1. A case of suspected relapse must be confirmed with a new biopsy, and obtaining a new biopsy should be considered in refractory disease

4.3.2. In some patients with a localized late relapse, salvage radiotherapy alone is likely to be sufficient (EL-3)[37]

4.3.3. In most patients with relapsed or refractory HL, the preferred treatment modality comprises platinum-based or brentuximab vedotin-containing regimen followed by high-dose chemotherapy and ASCT (EL-2).[38-48]

4.3.3.1 Salvage regimens such as GDP

(gemcitabine, dexamethasone, and cisplatin);[49] DICEP (dose-intensive cyclophosphamide, etoposide, cisplatin);[42,43] ESHAP (etoposide, methylprednisolone (solumedrol), high-dose cytarabine (ara-C) and cisplatin (platinum chemotherapy);[50] DHAP (dexamethasone, cytarabine, cisplatin);[40] IGEV (ifosfamide, gemcitabine, and vinorelbine);[41] ICE (ifosamide, carboplatin, and etoposide);[51] B-ICE (brentuximab vedotin plus ifosamide, carboplatin, and etoposide;[52] B-ESHAP (brentuximab vedotin plus etoposide, methylprednisolone (solumedrol), high-dose cytarabine (ara-C) and cisplatin (platinum chemotherapy);[53] BeGEV (bendamustine, gemcitabine and vinorelbine) or BvB (Brentuximab vedotin and bendamustine)[54,55] have been shown to reduce the disease burden and mobilize stem cells before high-dose chemotherapy and ASCT. However, no comparative trails have shown any salvage approach to be superior than the others (EL-2).

4.3.3.2. Several conditioning regimes such as BEAM (carmustine, etoposide, cytarabine, melphalan) or single agent high-dose melphalan have also been used (EL-3).[39,45-47]

4.3.3.3. The use of brentuximab vedotin as maintenance therapy for 1 year after ASCT is highly recommended for high-risk patients (primary refractory, patients who relapsed within 12 months, relapse with extra-nodal disease or pre-transplant positive PET/CT) (EL-2).[44,48]

4.3.4. Following ASCT, in responding patients found to have localized residual disease on PET, a consolidative radiotherapy to the active site is recommended (EL-3).

4.3.5. Patients who experience a relapse following ASCT have been shown to respond to the following treatment options (EL-2):

3.2.5.1. Brentuximab vedotin[55,56]

3.2.5.2. Nivolumab[57,58]

3.2.5.3. Pembrolizumab[59]

3.2.5.4. Allogeneic stem cell transplantation (in young patients with good general condition).[60]

5. MANAGEMENT OF NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA

NLPHL has a similar natural history to indolent lymphomas. As NLPHL cells consistently express CD20, addition of an anti-CD20 therapy improves treatment efficacy; currently, data provides support for the use of rituximab.[61]

5.1. Limited stage:

5.1.1. Observation is a reasonable option for completely excised lymph node

5.1.2. 30 Gy of ISRT (EL-3)[62]

5.1.3. Two to three cycles of combination chemotherapy (rituximab plus ABVD [R-ABVD], rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone [R-CHOP] or ABVD) with or without ISRT (EL-3).[62]

5.2. Advance stage:

5.2.1. The preferred option is combination chemotherapy (R-ABVD, R-CHOP or ABVD) for six cycles with or without ISRT (EL-3)[62]

5.2.2. Single-agent rituximab is recommended for patients who are unfit for cytotoxic chemotherapy.[63]

5.3. Relapsed (EL-3):[63-65]

5.3.1. A case of NLPHL relapse must be confirmed by a new biopsy before initiating salvage therapy to exclude transformation to aggressive non-HL

5.3.2. Individualized treatment should be considered because the natural history of the disease is variable

5.3.3. Localized NLPHL relapses can effectively be treated with rituximab with or without ISRT

5.3.4. Advanced disease at relapse often requires a more aggressive salvage therapy including high-dose chemotherapy and ASCT

5.3.5. Observation is a reasonable option for select asymptomatic patients.

6. TREATMENT RESPONSE EVALUATION AND LONG-TERM FOLLOW UP (EL-3)

6.1. The preferred imaging modality for assessing the response to therapy is PET/CT. This is typically first ("interim") done after the initial

two cycles of chemotherapy and 6–8 weeks after completing chemotherapy/ASCT or 8–12 weeks after completing radiotherapy. After completion of treatment, follow-up assessments are mainly focused on monitoring for recurrence and late side effects. In long-term survivors, the most serious late side effects are secondary cancers, hypothyroidism, cardiovascular diseases and fertility issues. The incidence of these late side effects is directly proportional to the duration of follow-up; nonetheless, the current treatment protocols are likely to have lesser side effects compared with those used >10 years ago. However, it is recommended that patients are encouraged to seek counseling regarding survivorship, long-term treatment effects, health habits and psychosocial issues.

6.1.1. The follow-up schedule after achieving remission:

6.1.1.1.1 Every 3 months for 2 years, then every 6 months for 3 years, and then annually

6.1.1.1.2. History and physical examination should be documented in every visit

6.1.1.1.3. CBC with differential count, erythrocyte sedimentation rate and LFT should be requested in every visit

6.1.1.1.4. TSH test should be carried out at least once annually if the patient received radiotherapy to the neck

6.1.1.1.5. Annual influenza immunization is recommended

6.1.1.1.6. Chest X-ray should be performed at each visit in the first 2 years, and then at every other visit, especially for patients who previously had intrathoracic disease

6.1.1.1.7. Mammogram or MRI of breast is required for women who received chest radiotherapy, beginning 10 years after diagnosis of lymphoma or when aged 40 years, whichever comes first

6.1.1.1.8. Pap smear is recommended.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Saudi Cancer Registry. Cancer Incidence Report in Saudi Arabia 2015. Riyadh (KSA): Saudi Cancer Registry; 2018.
2. Jazieh AR; Saudi Lung Cancer Guidelines Committee. The lung cancer management guidelines 2012. J Infect Public Health 2012;5 Suppl 1:S4-10.
3. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, *et al*. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 2014;32:3059-68.
4. El-Galaly TC, d'Amore F, Mylam KJ, de Nully Brown P, Bøgsted M, Bukh A, *et al*. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. J Clin Oncol 2012;30:4508-14.
5. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971;31:1860-1.
6. Caraway NP. Strategies to diagnose lymphoproliferative disorders by fine-needle aspiration by using ancillary studies. Cancer 2005;105:432-42.
7. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. J Clin Oncol 2004;22:3046-52.
8. Meda BA, Buss DH, Woodruff RD, Cappellari JO, Rainer RO, Powell BL, *et al*. Diagnosis and subclassification of primary and recurrent lymphoma. The usefulness and limitations of combined fine-needle aspiration cytomorphology and flow cytometry. Am J Clin Pathol 2000;113:688-99.
9. Henry-Amar M, Friedman S, Hayat M, Somers R, Meerwaldt JH, Carde P, *et al*. Erythrocyte sedimentation rate predicts early relapse and survival in early-stage Hodgkin disease. The EORTC lymphoma cooperative group. Ann Intern Med 1991;114:361-5.
10. Tubiana M, Henry-Amar M, Hayat M, Burgers M, Qasim M, Somers R, *et al*. Prognostic significance of the number of involved areas in the early stages of Hodgkin's disease. Cancer 1984;54:885-94.
11. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. N Engl J Med 1998;339:1506-14.
12. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al*. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (IARC WHO Classification of Tumours). Revised 4th ed. Lyon: International Agency for Research on Cancer; 2017.
13. Engert A, Plütschow A, Eich HT, Lohri A, Dörken B, Borchmann P, *et al*. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 2010;363:640-52.
14. Engert A, Schiller P, Josting A, Herrmann R, Koch P, Sieber M, *et al*. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: Results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 2003;21:3601-8.
15. Raemaekers JM, André MP, Federico M, Girinsky T, Oumedaly R, Brusamolino E, *et al*. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 2014;32:1188-94.
16. Sasse S, Klimm B, Görgen H, Fuchs M, Heyden-Honerkamp A, Lohri A, *et al*. Comparing long-term toxicity and efficacy of combined modality treatment including extended- or involved-field radiotherapy in early-stage Hodgkin's lymphoma. Ann Oncol 2012;23:2953-9.
17. Noordijk EM, Thomas J, Ferme C, Van't Veer MB, Brice P, Divine M, *et al*. First results of the EORTC-GELA H9 randomized trials: the H9-F trial (comparing 3 radiation dose levels) and H9-U

trial (comparing 3 chemotherapy schemes) in patients with favorable or unfavorable early stage Hodgkin's lymphoma (HL). J Clin Oncol 2005;23 Suppl 16:6505.
18. Eich HT, Diehl V, Görgen H, Pabst T, Markova J, Debus J, *et al*. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 2010;28:4199-206.
19. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer 2005;104:1066-74.
20. Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, *et al*. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015;372:1598-607.
21. Olszewski AJ, Shrestha R, Castillo JJ. Treatment selection and outcomes in early-stage classical Hodgkin lymphoma: Analysis of the national cancer data base. J Clin Oncol 2015;33:625-33.
22. Canellos GP, Abramson JS, Fisher DC, LaCasce AS. Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. J Clin Oncol 2010;28:1611-5.
23. Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Wells WA, Winter JN, *et al*. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 2012;366:399-408.
24. Landgren O, Axdorph U, Fears TR, Porwit-MacDonald A, Wedelin C, Björkholm M. A population-based cohort study on early-stage Hodgkin lymphoma treated with radiotherapy alone: With special reference to older patients. Ann Oncol 2006;17:1290-5.
25. Hoskin PJ, Lowry L, Horwich A, Jack A, Mead B, Hancock BW, *et al*. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group study ISRCTN 64141244. J Clin Oncol 2009;27:5390-6.
26. Johnson P, Federico M, Kirkwood A, Fosså A, Berkahn L, Carella A, *et al*. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med 2016;374:2419-29.
27. Barrington SF, Kirkwood AA, Franceschetto A, Fulham MJ, Roberts TH, Almquist H, *et al*. PET-CT for staging and early response: Results from the response-adapted therapy in advanced Hodgkin lymphoma study. Blood 2016;127:1531-8.
28. Engert A, Haverkamp H, Kobe C, Markova J, Renner C, Ho A, *et al*. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): A randomised, open-label, phase 3 non-inferiority trial. Lancet 2012;379:1791-9.
29. Carde P, Karrasch M, Fortpied C, Brice P, Khaled H, Casasnovas O, *et al*. Eight cycles of ABVD versus four cycles of BEACOPPescalated plus four cycles of BEACOPPbaseline in stage III to IV, international prognostic score ≥3, high-risk Hodgkin lymphoma: First results of the phase III EORTC 20012 intergroup trial. J Clin Oncol 2016;34:2028-36.
30. Mounier N, Brice P, Bologna S, Briere J, Gaillard I, Heczko M, *et al*. ABVD (8 cycles) versus BEACOPP (4 escalated cycles ≥4 baseline): Final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. Ann Oncol 2014;25:1622-8.
31. Viviani S, Zinzani PL, Rambaldi A, Brusamolino E, Levis A, Bonfante V, *et al*. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. N Engl J Med 2011;365:203-12.
32. Fabian CJ, Mansfield CM, Dahlberg S, Jones SE, Miller TP, Van Slyck E, *et al*. Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group Randomized study. Ann Intern Med 1994;120:903-12.
33. Aleman BM, Raemaekers JM, Tomišiĉ R, Baaijens MH, Bortolus R, Lybeert ML, *et al*. Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2007;67:19-30.
34. Johnson PW, Sydes MR, Hancock BW, Cullen M, Radford JA, Stenning SP. Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: Survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). J Clin Oncol 2010;28:3352-9.
35. Borchmann P, Haverkamp H, Diehl V, Cerny T, Markova J, Ho AD, *et al*. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: Final analysis of the HD12 trial of the German Hodgkin Study Group. J Clin Oncol 2011;29:4234-42.
36. Kriz J, Reinartz G, Dietlein M, Kobe C, Kuhnert G, Haverkamp H, *et al*. Relapse analysis of irradiated patients within the HD15 trial of the German Hodgkin Study Group. Int J Radiat Oncol Biol Phys 2015;92:46-53.
37. Josting A, Nogová L, Franklin J, Glossmann JP, Eich HT, Sieber M, *et al*. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: A retrospective analysis from the German Hodgkin Lymphoma Study Group. J Clin Oncol 2005;23:1522-9.
38. Carella AM, Bellei M, Brice P, Gisselbrecht C, Visani G, Colombat P, *et al*. High-dose therapy and autologous stem cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy: Long-term results. Haematologica 2009;94:146-8.
39. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, *et al*. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: A randomised trial. Lancet 2002;359:2065-71.
40. Josting A, Rudolph C, Reiser M, Mapara M, Sieber M, Kirchner HH, *et al*. Time-intensified dexamethasone/cisplatin/cytarabine: An effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol 2002;13:1628-35.
41. Santoro A, Magagnoli M, Spina M, Pinotti G, Siracusano L, Michieli M, *et al*. Ifosfamide, gemcitabine, and vinorelbine: A new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica 2007;92:35-41.
42. Shafey M, Duan Q, Russell J, Duggan P, Balogh A, Stewart DA. Double high-dose therapy with dose-intensive cyclophosphamide, etoposide, cisplatin (DICEP) followed by high-dose melphalan and autologous stem cell transplantation for relapsed/refractory Hodgkin lymphoma. Leuk Lymphoma 2012;53:596-602.
43. Al Garni A, Kaloyannidis P, Al Mulhem N, Al Hashmi H. DICEP is an effective chemotherapeutic regimen for patients with relapsed or refractory lymphomas who failed prior salvage chemotherapies. EHA Annual Meeting; Jun 9, 2016. p. Abstract 134620.
44. O'Connor OA, Lue JK, Sawas A, Amengual JE, Deng C, Kalac M, *et al*. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: An international, multicentre, single-arm, phase 1-2 trial. Lancet Oncol 2018;19:257-66.
45. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, *et al*. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: Results of a BNLI randomised trial. Lancet 1993;341:1051-4.
46. Stewart DA, Guo D, Sutherland JA, Ruether BA, Jones AR, Poon MC, *et al*. Single-agent high-dose melphalan salvage therapy for Hodgkin's disease: Cost, safety, and long-term efficacy. Ann Oncol 1997;8:1277-9.
47. Kaloyannidis P, Al Hashmi H, Rauf MS, Maghfoor I, Salman H, Kafnar S, *et al*. BEAM Versus Single Agent High Dose Melphalan (HDM) conditioning regimen for autologous hematopoietic stem cell transplant (ASCT): A retrospective matched analysis in relapse/refractory Hodgkin lymphoma. Biol Blood Marrow Transpl 2019;25:S187-8.
48. Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, *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;385:1853-62.
49. Moccia AA, Hitz F, Hoskins P, Klasa R, Power MM, Savage KJ, *et al*. Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated salvage therapy for relapsed/refractory diffuse large B-cell lymphoma and Hodgkin lymphoma. Leuk Lymphoma 2017;58:324-32.
50. Labrador J, Cabrero-Calvo M, Pérez-López E, Mateos MV, Vázquez L, Caballero MD, *et al*. ESHAP as salvage therapy for relapsed or refractory Hodgkin's lymphoma. Ann Hematol 2014;93:1745-53.
51. Moskowitz C. Risk-adapted therapy for relapsed and refractory lymphoma using ICE chemotherapy. Cancer Chemother Pharmacol 2002;49 Suppl 1:S9-12.
52. Moskowitz AJ, Schöder H, Yahalom J, McCall SJ, Fox SY, Gerecitano J, *et al*. PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: A non-randomised, open-label, single-centre, phase 2 study. Lancet Oncol 2015;16:284-92.
53. Garcia-Sanz R, Sureda A, Gonzalez, AP, De la Cruz F, Sanchez-Gonzalez B, Rodriguez A, *et al*. Brentuximab vedotin plus ESHAP (BRESHAP) is a highly effective combination for inducing remission in refractory and relapsed Hodgkin lymphoma patients prior to autologous stem cell transplant: A trial of the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO). Blood 2016;128:1109.
54. Santoro A, Mazza R, Pulsoni A, Re A, Bonfichi M, Zilioli VR, *et al*. Bendamustine in combination with gemcitabine and vinorelbine is an effective regimen as induction chemotherapy before autologous stem-cell transplantation for relapsed or refractory Hodgkin lymphoma: Final results of a multicenter phase II study. J Clin Oncol 2016;34:3293-9.
55. LaCasce AS, Bociek RG, Sawas A, Caimi P, Agura E, Matous J, *et al*. Brentuximab vedotin plus bendamustine: A highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood 2018;132:40-8.
56. Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, *et al*. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood 2016;128:1562-6.
57. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, *et al*. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311-9.
58. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, *et al*. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: A multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol 2016;17:1283-94.
59. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, *et al*. Phase II study of the efficacy and safety of pembrolizumab for relapsed/Refractory classic Hodgkin lymphoma. J Clin Oncol 2017;35:2125-32.
60. Sureda A, Canals C, Arranz R, Caballero D, Ribera JM, Brune M, *et al*. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study – A prospective clinical trial by the Grupo Español de linfomas/Trasplante de médula osea (GEL/TAMO) and the lymphoma working party of the European group for blood and marrow transplantation. Haematologica 2012;97:310-7.
61. Diehl V, Sextro M, Franklin J, Hansmann ML, Harris N, Jaffe E, *et al*. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: Report from the European task force on lymphoma project on lymphocyte-predominant Hodgkin's disease. J Clin Oncol 1999;17:776-83.
62. Nogová L, Reineke T, Eich HT, Josting A, Müller-Hermelink HK, Wingbermühle K, *et al*. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: A retrospective analysis from the German Hodgkin Study Group (GHSG). Ann Oncol 2005;16:1683-7.
63. Biasoli I, Stamatoullas A, Meignin V, Delmer A, Reman O, Morschhauser F, *et al*. Nodular, lymphocyte-predominant Hodgkin lymphoma: A long-term study and analysis of transformation to diffuse large B-cell lymphoma in a cohort of 164 patients from the Adult Lymphoma Study Group. Cancer 2010;116:631-9.
64. Al-Mansour M, Connors JM, Gascoyne RD, Skinnider B, Savage KJ. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. J Clin Oncol 2010;28:793-9.
65. Schulz H, Rehwald U, Morschhauser F, Elter T, Driessen C, Rüdiger T, *et al*. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: Long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). Blood 2008;111:109-11.