# Modern Management of Classical Hodgkin Lymphoma

PRESENTED BY AMY GOODRICH, CRNP, and JOSE D. SANDOVAL-SUS, MD

From Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland; and Moffitt Malignant Hematology and Cellular Therapy at Memorial Healthcare System, Tampa, Florida

Presenters' disclosures of conflicts of interest are found at the end of this article.

https://doi.org/10.6004/jadpro.2019.10.3.16



Many patients with classical Hodgkin lymphoma (cHL) have good outcomes, but some have a more challenging disease and require multiple lines of therapy. Fortunately, treatment options are growing. Since patients with relapsed or refractory HL are starting to have improved life expectancy, they may not only experience immediate treatment-related side effects, but also long-lasting risks and toxicities. Diligent management by advanced practitioners before, during, and after treatment may lessen these. According to information presented at JADPRO Live 2018 by Amy Goodrich, CRNP, of Johns Hopkins Kimmel Cancer Center, and Jose D. Sandoval-Sus, MD, from Moffitt Malignant Hematology and Cellular Therapy at Memorial Healthcare System, ongoing patient education and good communication with primary care providers and other specialists can help reduce the severity of adverse events and lessen their potential impact on quality of life.

"Hodgkin lymphoma is one of my favorite diseases [to treat], because it's usually very rewarding," said Dr. Sandoval-Sus. "With current treatments, we're curing 80% or more of these patients. There's still a fraction of patients who are not cured with front-line treatment, [but] they are benefiting from the new medications that we're developing."

## CLASSIFYING HODGKIN LYMPHOMA

Hodgkin lymphoma, which makes up only 0.5% of all new cancer cases in the United States, has a bimodal age distribution at diagnosis, with its first peak at age 20 and second peak at age 65. Survival is relatively good; by 2016, the 5-year overall survival rate exceeded 86% (National Cancer Institute, 2018). "It's a very curable malignancy, but we still lose some of our patients to this tumor," said Dr. Sandoval-Sus.

The World Health Organization recognizes five types of HL, but 95% is classified as cHL. Within this category there are four subtypes, classified according to differences in the appearance of the tumor cells and the composition of the microenvironment (Swerdlow et al., 2016): nodular sclerosis (typically characterized by mediastinal node involvement; more common in younger patients), mixed cellularity (more common in older patients), lymphocyte-rich (related to Epstein-Barr

J Adv Pract Oncol 2019;10(3):287–292

virus), and lymphocyte-depleted (rare; most common in patients with human immunodeficiency virus [HIV]).

## HODGKIN LYMPHOMA STAGING

Hodgkin lymphoma is generally divided into limited-stage disease (stages I and II) and advanced-stage disease (stages III and IV). Limited-stage HL is further divided into unfavorable and favorable risk, a classification that is particularly important to devise an appropriate treatment plan (i.e., bulky disease, extranodal involvement; National Comprehensive Cancer Network [NCCN], 2018), he noted.

The International Prognostic Score (IPS) for advanced-stage disease is commonly used in HL. It is only validated for stage III and IV HL, and assigns one point for each of 8 factors: albumin < 4 g/dL; hemoglobin < 10.5 g/dL; male sex; age ≥ 45 years; stage IV disease; leukocytosis; lymphocytopenia; and white blood cell and/or lymphocyte count < 600/mm$^3$ (Hasenclever et al., 1998). A score of zero is excellent, while a score ≥ 5 is considered high-risk or very high-risk disease. However, even among patients with a score ≥ 5, more than 40% are considered cured at 5 years.

## ABVD AS FRONT-LINE THERAPY

All regimens have related toxicities and can potentially cause significant side effects during and after therapy (see Table 1). Nonetheless, the majority of patients with cHL can be cured with initial therapy.

ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) is the most commonly used front-line treatment. It is usually administered for 2 to 6 cycles, depending on whether the patient has early- or advanced-stage disease (Engert et al., 2010).

Pretreatment screening is important. According to Ms. Goodrich, before starting treatment with ABVD, clinicians should test for HIV and hepatitis, educate patients on the risks of infertility and refer them to fertility counseling if necessary (Oktay et al., 2018), and assess cardiac function. For regimens that use bleomycin, a pulmonary function test with diffusing capacity of the lungs for carbon monoxide (DLCO) should be done. Dose adjustments for baseline liver or renal function may be necessary.

ABVD is a highly emetogenic regimen. "I'm sure you all have antiemetics regimens that you use," she said. "But it's not uncommon for patients to have to get stepped up or to need to have lorazepam added for their anticipatory nausea and vomiting." She advised assessing patients' level of nausea and vomiting frequency and premedicating with serotonin receptor (5-HT3) antagonists and steroids. Finally, clinicians should educate patients about the use of antiemetics and the importance of hydration, and encourage them to monitor fluid intake to prevent dehydration, she said.

Dr. Sandoval-Sus discourages the use of growth factors in patients on an ABVD regimen. "Bleomycin and growth factors have been related

**Table 1. Common Front-line Therapies Used in Classical Hodgkin Lymphoma**

| Regimen/Modality | Duration of therapy | Agents |
|---|---|---|
| ABVD | 2–6 cycles | Doxorubicin, bleomycin, vinblastine, dacarbazine |
| Stanford V | 8–12 weeks | Doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone |
| BEACOPP | 2–6 cycles | Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone |
| Involved site radiation therapy | Varies based on treatment location | |
| Brentuximab vedotin + AVD | Varies, used if stage III–IV, IPS > 4 or bleomycin contraindication | Brentuximab vedotin, doxorubicin, vinblastine, dacarbazine |

*Note.* IPS = International Prognostic Score. Information from Advani et al. (2013); Connors et al. (2018); Eich et al. (2010); Engert et al. (2010, 2012); NCCN (2018); Radford et al. (2015); Raemaekers et al. (2014); von Tresckow et al. (2012).

to more pulmonary toxicity," he said. "However, you should use growth factors if the patient develops febrile neutropenia."

For early-stage disease with unfavorable prognostic features, he recommends 6 cycles of ABVD with or without radiation therapy for bulky masses (≥ 10 cm). For localized disease with favorable prognostic features, he uses 4 cycles guided by results of an interim PET-CT with or without radiation therapy. Another option for early-stage disease with good prognostic features is 2 cycles of ABVD plus low-dose radiation, which he commented "works really well."

## OTHER FRONT-LINE THERAPIES IN CLASSICAL HODGKIN LYMPHOMA

The Stanford V is an older regimen, comprised of doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone, and is used for 8 to 12 weeks (Avandi et al., 2013). However, mechlorethamine has been associated with higher risks of infertility and secondary malignancies, he warned. Hence, it is not currently a preferred front-line regimen.

BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) is an important front-line regimen for advanced high-risk disease, typically used for 2 to 6 cycles. According to Dr. Sandoval-Sus, in high-risk patients with stage III or IV disease who have undergone 2 cycles of ABVD and still have positive PET-CT scans, continued therapy with standard or escalated BEACOPP is a viable treatment option (von Tresckow et al., 2012), but being another chemotherapy-heavy regimen, it is also related to a higher incidence of secondary malignancies.

"I only use it in patients who are young and have good performance status," he noted. "It's a hard therapy to use. It's very effective, but it has its own implications."

"We use it when we have to," Ms. Goodrich added. "Treatment-related mortality is quite startling in older [patients]" (Wongso et al., 2013).

Involved-site radiation therapy paired with chemotherapy is another common front-line therapy. "I would say that radiation is unpopular here in the United States, but I believe it's very important, especially for patients with limited-stage disease, and particularly for men," he said.

Recently approved by the US Food and Drug Administration (FDA), brentuximab vedotin plus AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) is a "new kid on the block" for front-line treatment. It is approved for stage III or IV disease, and for patients with International Prognostic Score > 4. Dr. Sandoval-Sus cautioned that brentuximab vedotin should never be used with bleomycin, "because the pulmonary toxicity is prohibitive."

## GENERAL PRINCIPLES OF TREATMENT FOR RELAPSED AND REFRACTORY HODGKIN LYMPHOMA

For patients with relapsed or refractory disease, treatment depends largely on the pattern of relapse and the agents previously used. Autologous hematopoietic stem cell transplant (HSCT) should be considered for transplant-eligible patients who achieve a complete or partial response with second-line treatment, while allogeneic HSCT (alloHSCT) may be considered in eligible patients who fail autologous HSCT and respond to third-line treatment (NCCN, 2018). Nonetheless, alloHSCT is currently a controversial topic in HL due to the excellent outcomes with newly approved agents.

Brentuximab vedotin is a treatment option if autologous HSCT or at least two prior multiagent chemotherapy regimens have failed. Brentuximab with or without chemotherapy can be used as second-line therapy prior to autologous HSCT to minimize the use of more intensive chemotherapy (NCCN, 2018). According to Dr. Sandoval-Sus, brentuximab vedotin maintenance after autologous HSCT needs to be considered in patients who fulfill one or more of the following criteria: relapse < 12 months after initial remission, primary refractory disease, or relapse with extranodal disease.

It is important to note that around 60% of patients on brentuximab vedotin are likely to develop some degree of peripheral neuropathy (Table 2). This condition is common in cHL due to the use of neurotoxic agents, and it can last for days, months, or years, or even be permanent (Hershman et al., 2014). "There have been countless studies trying to prevent peripheral neuropathy. Nothing has worked, and so there is no prevention for it other than early detection and appropriate management from there," said Ms. Goodrich. "I'm looking for-

**Table 2. Toxicities of Brentuximab Vedotin**

| Toxicity | Overall (%) | Grades 3/4 (%) |
|---|---|---|
| *Blood and lymphatic system* | | |
| Neutropenia | 55 | 21 |
| Anemia | 52 | 2 |
| Thrombocytopenia | 16 | 10 |
| *Nervous system disorders* | | |
| Peripheral sensory neuropathy | 53 | 10 |
| Peripheral motor neuropathy | 7 | 3 |
| *General disorders and administration site reactions* | | |
| Fatigue | 41 | 4 |
| Pyrexia | 38 | 2 |
| Pain | 28 | 5 |
| Peripheral edema | 16 | 0 |
| *Gastrointestinal disorders* | | |
| Nausea | 38 | 2 |
| Diarrhea | 29 | 3 |
| *Skin and subcutaneous tissue disorders* | | |
| Rash | 31 | 0 |

*Note.* Information from Seattle Genetics, Inc. (2018).

ward to somebody fixing that." Other common toxicities associated with brentuximab vedotin are fatigue, pyrexia, nausea, diarrhea, and bowel changes.

## CHECKPOINT INHIBITORS

According to Dr. Sandoval-Sus, HL is "the cancer that has the best response to checkpoint inhibitors." Nivolumab (Opdivo) and pembrolizumab (Keytruda) are options for cHL that has relapsed or progressed following autologous HSCT and brentuximab vedotin.

A phase I study that enrolled 104 patients with hematologic malignancies (23 with relapsed/refractory HL; 78% postautologous transplant and 78% postbrentuximab) found an overall response rate of 87% to nivolumab (Ansell et al., 2015). At 7 years, 5 of the patients with Hodgkin lymphoma had progressed, 5 went on to transplant, and 10 are still responding. "This really revolutionized the care of these patients who we had nothing for just 5 years ago," she added.

Pembrolizumab was approved for HL in 2017. It is approved for adult and pediatric patients with refractory disease, and for adult and pediatric patients who have relapsed after ≥ 3 prior lines of therapy. In a heavily pretreated population in the KEYNOTE-087 trial, overall response rates to pembrolizumab were 73% for patients who underwent transplant and received brentuximab, 64% for patients who were ineligible for transplant and had progressed after brentuximab, and 70% for patients who underwent transplant but did not receive posttransplant brentuximab (Moskowitz et al., 2016). "All of those numbers are really quite impressive," Ms. Goodrich noted.

## KEYS TO OPTIMAL MANAGEMENT OF PATIENTS ON IMMUNE CHECKPOINT INHIBITORS

Providers should be aware that the onset of adverse events associated with immune checkpoint inhibition is variable and can affect any organ system. The time to onset of adverse events is typically delayed; therefore, the health-care team, patients, and caregivers should be educated on the often-subtle symptoms at initial presentation (Table 3).

"Depending on which adverse event patients are having, you can use a different mix of these agents," she explained. "The key is tapering patients off of high-dose steroids slowly, and if they flare, reescalating the steroids to try to get things under control again."

Checkpoint inhibitors cause unique side effects, so rapid and timely intervention is crucial. Steroids are the cornerstone for some intolerable grade 2 side effects and any grade 3 or 4 immune-related adverse events. Steroids should be slowly tapered over 4 to 6 weeks. Reinitiation of anticancer treatment may be possible, particularly when using programmed cell death protein 1 (PD-1) inhibitors (Dadu, Zobniw, & Diab, 2016).

Importantly, transplant-related deaths have occurred in patients receiving salvage checkpoint inhibitors prior to alloHSCT. It is crucial to monitor closely for hyperacute graft-vs.-host disease (GVHD), severe (grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions (Merck Sharp & Dohme Corp., 2019). Effective contraception is also important for patients receiving any time of treatment for HL.

**Table 3. Treatment of Severe and Steroid-Refractory Immune-Related Adverse Events**

| Type and severity of irAE | Initial management | Additional immunosuppression | Immunosuppression tapering schedule |
|---|---|---|---|
| **Colitis and/or diarrhea** (grade 3–4)<br>• Increase of ≥ 7 stools per day over baseline<br>• Abdominal pain, fever, and change in bowel habits | • Admit to hospital for intravenous corticosteroid therapy (methylprednisolone 1–2 mg/kg daily dose)<br>• Supportive care including intravenous fluids, supplemental oxygen, and antibiotics as needed<br>• Withhold hepatotoxic drugs<br>• Consider further diagnostic imaging or procedures | **Colitis and/or diarrhea**<br>• If no improvement after 3 days, give infliximab 5 mg/kg<br>• Can redose infliximab after 2 weeks if needed | **Colitis and/or diarrhea**<br>• Rapidly tapering course of steroids as tolerated over 4–6 weeks<br>• Increase steroids if diarrhea flares and then restart tapering |
| **Hepatitis** (grade 3–4)<br>• AST and/or ALT levels > 5 × ULN<br>• Total bilirubin level > 3 × ULN | | **Hepatitis**<br>• If no improvement after 3 days, start mycophenolate mofetil 500–1,000 mg every 12 hours | **Hepatitis**<br>• Rapidly tapering course of steroids as tolerated; discontinue mycophenolate mofetil once tapered to prednisone 10 mg daily |
| **Pneumonitis** (grade 3–4)<br>• Severe, life-threatening symptoms<br>• Worsening hypoxia | | **Pneumonitis**<br>• If no improvement after 48 hours, start additional agent as above or cyclophosphamide | **Pneumonitis**<br>• Taper steroids slowly over 6 weeks<br>• Mycophenolate mofetil management as above if needed |

*Note.* AST = aspartate transaminase; ALT = alanine transaminase; ULN = upper limit of normal. Adapted from Friedman, Proverbs-Singh, and Postow (2016).

## SECOND-LINE THERAPIES AND BEYOND FOR RELAPSED/ REFRACTORY HODGKIN LYMPHOMA

"In second-line therapy and beyond, we now have options," Ms. Goodrich said, noting that today's patients often receive multiple lines of treatment.

Advanced practitioners play a critical role in educating patients, their families, and their caretakers along this journey. They should participate in shared decision-making regarding treatment options, side effects, and impact on quality of life, and should monitor and manage regimen-specific side effects for current and prior regimens, said Ms. Goodrich.

Compared to the general population, HL patients have a greatly increased risk of developing secondary malignancies. One in 5 survivors will develop a second cancer within 20 years of treatment. Because of this risk, patients should not smoke and should avoid secondary smoke, and women treated with chest radiation before the age of 30 should get early breast cancer screening. Five to 8 years postradiation or at age 25 (whichever is later), women should receive regular breast exams, mammograms, and yearly magnetic resonance imaging of the breast (Children's Oncology Group, 2018). "This is an important part of their survivorship care plans and their primary care," she said, "but gynecologists may not know this, if we don't tell them."

"We're curing over 80% of these patients, so it's an excellent time to be treating and following these patients through treatment. This is the type of patient that you can see go to college, graduate, have a family," added Dr. Sandoval-Sus. "It's very gratifying to treat the patient when all goes well. The other 20% are still very challenging and we continue to work eagerly in order to improve their outcomes."

### Disclosure

Ms. Goodrich and Dr. Sandoval-Sus have no conflicts of interest to disclose.

### References

Advani, R. H., Hoppe, R. T., Baer, D., Mason, J., Warnke, R., Allen, J.,...Horning, S. J. (2013). Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: Mature results of the G4 trial. *Annals of Oncology, 24*(4), 1044–1048. https://doi.org/10.1093/annonc/mds542

Ansell, S. M., Lesokhin, A. M., Borrello, I., Halwani, A., Scott, E. C., Gutierrez, M.,...Armand, P. (2015). PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lym-

phoma. *New England Journal of Medicine, 372*(4), 311–319. https://doi.org/10.1056/NEJMoa1411087

Children's Oncology Group (2018). Long-Term Follow-Up Guidelines, version 5.0. Retrieved from http://www.survivorshipguidelines.org/

Connors, J. M., Jurczak, W., Straus, D. J., Ansell, S. M., Kim, W. S., Gallamini, A.,...Radford, J. (2018). Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *New England Journal of Medicine, 378*(4), 331–344. https://doi.org/10.1056/NEJMoa1708984

Dadu, R., Zobniw, D., & Diab, A. (2016). Managing adverse events with immune checkpoint agents. *The Cancer Journal, 22*(2), 121–129. https://doi.org/10.1097/PPO.0000000000000186

Eich, H. T., Diehl, V., Görgen, H., Pabst, T., Markova, J., Debus, J.,...Engert A. (2010). 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. *Journal of Clinical Oncology, 28*(27), 4199–4206. https://doi.org/10.1200/JCO.2010.29.8018

Engert, A., Haverkamp, H., Kobe, C., Markova, J., Renner, C., Ho, A.,...Diehl, V. (2012). 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, 379*(9828), 1791–1799. https://doi.org/10.1016/S0140-6736(11)61940-5

Engert, A., Plütschow, A., Eich, H. T., Lohri, A., Dörken, B., Borchmann, P.,...Diehl, V. (2010). Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *New England Journal of Medicine, 363*(7), 640–652. https://doi.org/10.1056/NEJMoa1000067

Friedman, C.F., Proverbs-Singh, T. A., & Postow, M. A. (2016). Treatment of the immune-related adverse effects of immune checkpoint inhibitors: A review. *JAMA Oncology, 2*(10), 1346–1353. https://doi.org/10.1001/jamaoncol.2016.1051.

Hasenclever, D., Diehl, V., Armitage, J. O., Assouline, D., Björkholm, M., Brusamolino, E.,...Hudson, G. V. (1998). A prognostic score for advanced Hodgkin's disease. *New England Journal of Medicine, 339*(21), 1506–1514. https://doi.org/10.1056/NEJM199811193392104

Hershman, D. L., Lacchetti, C., Dworkin, R. H., Lavoie Smith, E. M., Bleeker, J., Cavaletti, G.,...Loprinzi, C. L. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology, 32*(18), 1941–1967. https://doi.org/10.1200/JCO.2013.54.0914

Merck Sharp & Dohme Corp. (2019). Keytruda (pembrolizumab) package insert. Retrieved from https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

Moskowitz, C. H., Luigi Zinzani, P., Fanale, M. A., Armand, P., Johnson, N. A., Radford, J. A.,...Chen, R. W. (2016). Pembrolizumab in relapsed/refractory classical hodgkin lymphoma: Primary end point analysis of the phase 2 Keynote-087 study. *Blood, 128*(22), 1107. Retrieved from http://www.bloodjournal.org/content/128/22/1107?sso-checked=true

National Cancer Institute. (2018). Surveillance, Epidemiology, and End Results Program: Cancer Stat Facts: Hodgkin lymphoma. Retrieved from https://seer.cancer.gov/statfacts/html/hodg.html

National Comprehensive Cancer Network. (2018). NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma. v3.0. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf

Oktay, K., Harvey, B. E., Partridge, A. H., Quinn, G. P., Reinecke, J., Taylor, H. S.,...Loren, A. W. (2018). Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update. *Journal of Clinical Oncology, 36*(19), 1994–2001. https://doi.org/10.1200/JCO.2018.78.1914

Radford, J., Illidge, T., Counsell, M., Hancock, B., Pettengell, R., Johnson, P.,...Barrington, S. (2015). Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *New England Journal of Medicine, 372*(17), 1598–1607. https://doi.org/10.1056/NEJMoa1408648.

Raemaekers, J. M., André, M. P., Federico, M., Girinsky, T., Oumedaly, R., Brusamolino, E.,...Fortpied C. (2014). 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. *Journal of Clinical Oncology, 32*(12), 1188–1194. https://doi.org/10.1200/JCO.2013.51.9298

Seattle Genetics, Inc. (2018). Adcetris (brentuximab vedotin) package insert. Retrieved from https://www.adcetris.com/pi

Swerdlow, S. H., Campo, E., Pileri, S. A., Harris, N. L., Stein, H., Siebert, R.,...Jaffe, E. S. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood, 127*(20), 2375–2390. https://doi.org/10.1182/blood-2016-01-643569

von Tresckow, B., Plütschow, A., Fuchs, M., Klimm, B., Markova, J., Lohri, A.,...Engert, A. (2012). Dose-intensification in early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD14 trial. *Journal of Clinical Oncology, 30*(9), 907–913. https://doi.org/10.1200/JCO.2011.38.5807

Wongso, D., Fuchs, M., Plütschow, A., Klimm, B., Sasse, S., Hertenstein, B.,...Engert, A. (2013). Treatment-related mortality in patients with advanced-stage Hodgkin lymphoma: An analysis of the German Hodgkin Study Group. *Journal of Clinical Oncology, 31*(22), 2819–2824. https://doi.org/10.1200/JCO.2012.47.9774