Strategies for Management of Relapsed or Refractory Hodgkin Lymphoma

Presented by Leo I. Gordon, MD

Abstract

The advent of effective therapies has improved outcomes for those with newly diagnosed Hodgkin lymphoma (HL), with a resulting cure rate of at least 80%. However, with limited data on therapeutic options in the setting of advanced disease, individualized treatment is recommended, and potential long-term effects of therapy remain a key consideration. At the NCCN 22nd Annual Conference, Dr. Leo I. Gordon explored strategies for systemic therapy in the relapsed or refractory setting, focusing primarily on the standard of high-dose therapy/autologous stem cell rescue, the CD30-targeted antibody drug conjugate brentuximab vedotin, and checkpoint inhibition.

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There are a number of salvage chemotherapy regimens in relapsed or refractory [R/R] Hodgkin lymphoma [HL],” revealed Leo I. Gordon, MD, Abby and John Friend Professor of Cancer Research and Professor of Medicine, Division of Hematology/Oncology, Robert H. Lurie Comprehensive Cancer Center. “The concept here is to use a regimen that achieves as close to a complete response [CR] as possible,” he added. Dr. Gordon is Vice Chair of the NCCN Non-Hodgkin’s Lymphomas Panel and a member of the NCCN Hodgkin Lymphoma Panel.

To begin, several prognostic factors should be considered in R/R HL, including time to relapse (<3 months suggests primary refractory disease; 3–12 months indicates early relapse), advanced disease stage, and poor performance status. Other negative factors include a low albumin level, anemia, age, lymphocytopenia, extranodal disease, and disease status at transplant.

According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), second-line systemic therapy is appropriate for any patient with

relapsed disease, regardless of the length of initial remission. Therapy may be given before high-dose therapy/autologous stem cell rescue (HDT/ASCR), with or without radiation therapy.

“The idea of using radiation therapy alone is not a curative option, but a very reasonable palliative approach,” according to Dr. Gordon. In selected patients who have long disease-free intervals and other favorable features, selection of second-line therapy should be individualized, based on NCCN recommendations. Dr. Gordon stressed the importance of performing a biopsy to confirm suspected relapse.

Transplant Remains the Standard Approach

HDT/ASCR remains the best treatment approach for patients with R/R classical HL, according to the NCCN Guidelines. There are several salvage chemotherapy regimens, and Dr. Gordon noted that the most commonly used one is either ICE (ifosfamide, carboplatin, etoposide) or DHAP (dexamethasone, high-dose cytarabine, cisplatin). However, he admitted, data exist only on a relatively small number of patients.

High-dose chemotherapy and transplantation remain the standard approach in the R/R disease setting, and this recommendation is based on an older study by Schmitz et al.¹ In this randomized trial, the high-dose regimen consisted of BEAM (carmustine, etoposide, cytarabine, melphalan) in combination with autologous

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hematopoietic stem cell transplantation (SCT). “Clearly, there was an improvement with high-dose chemotherapy and transplant compared with conventional chemotherapy,” Dr. Gordon noted. With this approach, approximately 60% of patients with chemosensitive first relapse of HL were free from treatment failure—a “striking difference in outcomes” compared with patients with chemorefractory disease before transplant.

“For patients who are failing to achieve complete or very good partial remission,” suggested Dr. Gordon, “one should begin considering allogeneic transplant.”

The benefits of allogeneic transplant in chemotherapy sensitive patients before transplant were confirmed in another study, which used a low-intensity regimen of fludarabine and melphalan.² In this population of 92 heavily pretreated patients, allogeneic SCT resulted in long-term progression-free survival (PFS). For the allografted population, nonrelapse mortality at approximately 4 years was 19% (at 100 days, it was 8%). “It is important to look beyond 1 year to see the late effects of allogeneic transplant,” Dr. Gordon urged.

Brentuximab Vedotin

Other therapies target the hepatocyte growth factor–regulated tyrosine kinase substrate (HRS) receptors, such as CD30, CD40, Trail (Apo2L), interleukin-13, and CD80 (Table 1).

Maintenance therapy with the CD30-targeted antibody drug conjugate brentuximab vedotin after HDT/ASCR is included as an option in the NCCN Guidelines for patients with primary refractory disease. This recommendation is based on the randomized phase III AETHERA trial,³ which showed that early consolidation with brentuximab vedotin after autologous SCT improved PFS in patients with HL who had high-risk factors for relapse or disease progression after transplantation.

“This study led to the approval of brentuximab vedotin in the maintenance setting,” mentioned Dr. Gordon. “If you look out to 40 months and beyond, these curves [those free of progressive disease or death] are starting to come together,” suggesting that there was less of a difference over time.

A closer look at the study results showed that PET scan can be a predictive factor in the use of

this agent. “In patients who had a negative PET scan before transplant, the difference between brentuximab vedotin and placebo is negligible,” Dr. Gordon revealed. He offered the following suggestion for considering brentuximab vedotin in the real-world clinical setting: “For patients whose disease might not be in remission going into transplant or who are not clearly in remission after transplant, there is an advantage to giving another active agent in HL. But for those who may be at high risk but still were PET-negative going into transplant, it [the benefit of another agent] isn’t as clear to me.”

Checkpoint Inhibition

Dr. Gordon focused his discussion primarily on 2 recent studies with the checkpoint inhibitor nivolumab in advanced disease.

In the first trial by Ansell et al,⁴ 23 heavily treated patients with R/R HL received nivolumab, and >75% of patients were enrolled on the study after a relapse following allogeneic SCT. The overall response rate was 87%, which Dr. Gordon called “fairly exciting data in a small number of patients, most of whom were naïve to brentuximab vedotin.” However, he noted, there were few CRs (17%).

Table 1. Targeted Agents in Hodgkin Lymphoma

Targeting HRS receptors
CD30
CD40
Trail (Apo2L) and receptors
Interleukin-13 and receptors
CD80 (B7.1)
Targeting intracellular survival pathways with small molecules
Histone deacetylase (HDAC) inhibitors
PI3K/Akt/mTOR
Nuclear factor-kappa B (NF-κB)
Heat shock protein 90
Targeting the microenvironment
Rituximab
Lenalidomide
Auto LMP2-cytotoxic T cells for Epstein Barr virus-positive disease

Gordon

Figure 1. Management of recurrent/refractory Hodgkin lymphoma. Abbreviations: auto, autologous; CR, complete response; DHAP, dexamethasone/cisplatin/high-dose cytarabine; ESHAP, etoposide/methylprednisolone/high-dose cytarabine/cisplatin; ICE, ifosfamide/carboplatin/etoposide; VGPR, very good partial response.

In the follow up multicenter phase II trial by Younes et al (CheckMate 205),⁵ the use of nivolumab resulted in frequent responses in patients with recurrent classical HL whose disease had failed to respond to allogeneic SCT and had either relapsed after or failed to respond to brentuximab vedotin. Again, the CR rates were disappointing, and there was a falloff in PFS at approximately 6 months. “Clearly, we need to do better,” Dr. Gordon acknowledged. “It may be that with immunotherapy, our holy grail of CR may not have the same meaning as it has traditionally been used,” he added.

Dr. Gordon concluded his presentation with a look at 2 studies exploring the role of allogeneic transplant in the era of programmed cell death protein-1 (PD-1) blockade in classical HL.^{6,7} The first study asked whether allogeneic transplant can safely be performed after PD-1 blockade. According to the findings of a group from Dana-Farber Cancer Institute,⁶ the answer seems to be yes, with a “fairly acceptable” incidence of relapse reported for a high-risk group of patients with R/R disease.

However, an increased risk of early immune toxicity is concerning with this therapeutic strategy, and might reflect long-lasting immune alterations triggered by a prior PD-1 blockade.⁶ In this study, >70% of patients had graft-versus-host disease (GVHD). “We have to be very cautious about routinely performing an allogeneic SCT after checkpoint inhibitor therapy,” warned Dr. Gordon.

The second trial asked whether PD-1 blockade could be safely performed after allogeneic SCT.⁷ Again, the answer seems to be yes: in this small study of 12 patients with R/R HL, nivolumab was effective, with 7 of 8 evaluated patients experiencing a response (3 CRs and 4 partial responses). However, again, acute GVHD was observed in 2 patients after 1 to 2 injections of nivolumab.

A summary of the management algorithm for patients with R/R classical HL is presented in Figure 1.

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