Optimizing First-Line Therapy for Advanced-Stage Classic Hodgkin Lymphoma

Presented by Ranjana H. Advani, MD

ABSTRACT

Goals of first-line therapy in classic Hodgkin lymphoma (cHL) should focus on balancing risk versus benefit to the individual while increasing efficacy and decreasing toxicity. Overall, the ABVD regimen is well tolerated but slightly less effective, with a better safety profile compared with escalated BEACOPP. BV-AVD is somewhere in between ABVD and escalated BEACOPP on the cure/morbidity scale. Interim PET is predictive, but new prognostic biomarkers are emerging that may better identify patients at high risk for treatment failure. In patients with interim PET-negative cHL, de-escalating therapy does not impact overall survival along 1) with no proven role for radiotherapy. cHL is largely a disease of young people, and the choice of treatment should always take into account the potential for both short- and long-term toxicity with the goal of optimizing survivorship.

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Optimizing first-line therapy for advanced-stage classic Hodgkin lymphoma (cHL) comes down to balancing risk with benefit to the individual, according to Ranjana H. Advani, MD, Saul A. Rosenberg Professor of Lymphoma, Stanford Cancer Institute, at the NCCN 2021 Virtual Congress: Hematologic Malignancies. Optimal care for cHL should aim to increase efficacy and decrease toxicity through a combination of risk-adapted and response-adapted therapies, while also employing an optimal survivorship plan and following patients through the continuum of care.

cHL represents approximately 10% of all lymphomas, with approximately 9,000 new cases each year in the United States.¹ It is highly curable with frontline therapy, even in advanced-stage disease, and at any given time more cured survivors exist than do patients with active disease. The cure rate with most current approaches ranges from 75% to 85%.^{2,3} “So, the therapeutic priority, as well as the research priority, is focused on how to increase efficacy but to also decrease toxicity, in both the short and the long term,” said Dr. Advani.

According to Dr. Advani, the dilemma of therapy over the past decade has centered around the choice of ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) versus escalated BEACOPP (bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone). “ABVD was better tolerated than the escalated BEACOPP regimen, despite the fact that it may have slightly less efficacy than escalated BEACOPP,” she said. “A lot of the research trials tried to determine if we could distinguish ‘very bad’ disease from ‘less bad’ disease, and interim PET scans proved to be that tool.”

Interim PET

Interim PET scans can act as an early biomarker of resistant disease. The last decade of trials in the field have focused on interim PET-based modification of therapy, which has allowed for either treatment de-escalation or escalation.

Key trials have employed 2 strategies for initial therapy (for most studies of advanced-stage disease, a Deauville score >3 was considered positive; of note, many studies also included patients with stage IIBX disease)^{4–6}: (1) start with ABVD and escalate or de-escalate therapy based on interim PET after 2 cycles, or (2) start with escalated BEACOPP and escalate or de-escalate therapy based on interim PET after 2 cycles.

The RATHL trial showed that for patients who were PET-negative after 2 cycles of ABVD (Deauville score 1–3) bleomycin can be safely omitted from subsequent cycles, according to Dr. Advani, with excellent progression-free survival (PFS) and overall survival (OS).^{2,7,8} Across the various trials, patients who were PET-positive after 2 cycles of ABVD and switched to escalated BEACOPP, PFS rates were between 60% and 70%. “Compared to historical data of patients who continued on ABVD, these outcomes were more robust,” she noted.

According to Dr. Advani, the Italian strategy, which switched patients on ABVD to transplantation after a PET-positive scan, has also demonstrated excellent results, with a 2-year PFS of 75% after switching to transplantation.⁵

End of Treatment PET

End of therapy PET imaging is also important for both PFS and OS, Dr. Advani said.⁹ “The worst outcome is if a

patient is PET-positive at the end of therapy,” she noted. “Approximately 8% to 10% of patients may have been interim PET-negative but are then PET-positive at the end of therapy, and they do pretty poorly. So, I think it is important to do [a PET scan] at the end of therapy as well.”

For patients with advanced stage disease and who are PET-negative (interim and end-of-treatment), studies show no role for radiotherapy—even in bulky disease.¹⁰

Lessons Learned

According to Dr. Advani, the SWOG 0816 study demonstrated the various strengths and limitations of a PET-adapted approach to treatment for stage III–IV cHL. First, relapses and second cancers occur late in patients with cHL, thus long-term follow-up reports are crucial to fully interpret study results. Early PET response-adapted ABVD-based therapy for cHL results in improved outcomes for early interim PET-positive patients, and in excellent overall outcomes.

“We also learned that interim PET is not perfect,” commented Dr. Advani. “There’s a higher rate of false-negative results; therefore, more sensitive tools for detection of residual unresponsive disease are needed.”

Finally, end-of-treatment PET/CT remains necessary to identify patients with primary refractory disease who may require expedited salvage therapy.

Mitigating Toxicity to Gonadal Function

“Hodgkin lymphoma is a disease of young people, and we like to preserve fertility,” said Dr. Advani. “That’s why ABVD has stood the test of time, because most patients do not lose their fertility with this treatment.”

Gonadal function in female patients recovers to baseline levels more quickly in those who stay on ABVD versus escalated BEACOPP. Similarly, the recovery of follicle-stimulating hormone (FSH) to premenopausal levels is much higher in patients on ABVD versus escalated BEACOPP. However, age also may play a huge role: patients aged >35 years who receive BEACOPP have an even higher risk of infertility.¹¹

The AHL2011 trial also examined gonadal function recovery.¹² The standard group received 6 cycles of escalated BEACOPP, whereas the study group was de-escalated to ABVD. At the end of chemotherapy, FSH levels were high in both groups, but in time, FSH and anti-Müllerian hormone levels, sperm counts, and sperm motility returned to normal in the study group. The proportion of patients who recovered ovarian function was also higher in the study group, in which therapy was de-escalated.

The ECHELON-1 trial evaluated the incorporation of brentuximab vedotin (BV) + AVD (doxorubicin/vinblastine/dacarbazine) versus ABVD; this trial design was not based on interim PET findings.³ A 5-year update of the

trial revealed a PFS advantage of approximately 7% to 8% in patients who received BV + AVD. PET2-negative patients given BV + AVD had a 5-year PFS of 84.9% versus 78.9% with ABVD, and this difference was statistically significant ($P=.0035$).

Summary of Current Strategies in Advanced cHL

Interim PET is predictive, and the negative predictive value is higher with more intense therapies like escalated BEACOPP, and de-escalation of therapy does not impact OS, Dr. Advani reiterated. “You can drop down to ABVD after BEACOPP, and OS will not be impacted,” she noted. “And escalation of therapy if interim PET is positive after 2 rounds of ABVD is also a promising approach.”

Bleomycin can be omitted after 2 cycles of ABVD if PET is negative, and using BV instead of bleomycin results in an approximately 7% improvement in PFS at 5 years. “This doesn’t result in an OS difference, but there is no increase in infertility or secondary malignancy,” she added. In interim PET-negative patients, 4 cycles of escalated BEACOPP is just as good as 6 cycles, according to Dr. Advani. “You do not need to use anything beyond 4,” she stressed.

Dr. Advani noted that currently, no randomized controlled trials of escalation therapy have been conducted using a true randomization between a PET-adapted (escalated arm) and a standard control arm using the ABVD regimen.

Treatment options for patients with advanced-stage cHL are summarized in Figure 1. “The dilemma of therapy continues,” said Dr. Advani. “ABVD is probably the easiest regimen, with the least amount of toxicity; escalated BEACOPP is probably the most effective, but with more toxicity; and BV + AVD falls somewhere in between.” She added that escalated BEACOPP or BV-based regimens have not been adopted widely in the United States for several reasons. To begin, there is no OS advantage and more toxicity with these regimens, Dr. Advani said, but another important factor is their high cost. One cost-effectiveness analysis of BV with chemotherapy in newly diagnosed stage III and IV cHL showed that a 6-month treatment course of ABVD totaled \$3,648 compared with \$284,616 for 6 months of BV + AVD.¹³

Moving Checkpoint Inhibitors to the Front Line

Due to an improved understanding of tumor biology in recent years, research into immune checkpoint inhibitors (ICIs) has led to the approval of nivolumab and pembrolizumab for relapsed cHL.

A phase III randomized trial is currently underway comparing nivolumab and AVD with BV + AVD in patients aged >12 years with newly diagnosed advanced-stage cHL (ClinicalTrials.gov identifier: NCT03907488). The rationale for this trial was based on promising

Figure 1. Clinical presentation: stage III–IV cHL (HODG-5). From the NCCN Guidelines for Hodgkin Lymphoma. Version 4.2021. To view the most recent version, visit NCCN.org.

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findings from a phase II study in which no significant differences were observed between PET-negative and PET-positive patients when nivolumab was added to AVD.¹⁴

A phase II study of PET-directed frontline therapy with sequential pembrolizumab + AVD for patients with cHL has also shown great promise. At 22 months, investigators observed a 100% PFS rate, with no increased toxicity, prompting a global study of this regimen in the frontline setting (NCT03226249).

“Currently, there’s a lot of excitement in the field about moving ICIs to the frontline setting,” Dr. Advani said. Ongoing trials of ICIs in the frontline setting are being explored.

Emerging Prognostic Markers in cHL

Beyond interim PET, certain prognostic markers can be used to identify patients at high risk of treatment failure. In the HD06/07 study, reduction in early serum levels of thymus and activation-regulated chemokine (TARC) predicted prognosis in patients with advanced cHL treated with a PET-adapted strategy.¹⁵ Patients with high serum TARC levels (>800 pg/mL) after 2 cycles of ABVD had worse outcomes than those with lower serum TARC levels, even in patients with a negative PET2 result. According to Dr. Advani, this may constitute a biomarker that can identify patients with chemosensitive disease.

Another study found that interim serum TARC levels may more accurately reflect treatment response and may have a higher positive predictive value than interim PET.¹⁶ “The jury is still out because these studies are small, but these data are certainly interesting and provocative,” she added.

Baseline metabolic tumor volume (MTV) has now been shown in several studies to predict treatment failure after ABVD. In a retrospective analysis of the GITIL/FIL HD0607 trial,¹⁷ baseline MTV and International Prognostic Score (IPS) combined predicted ABVD failure in patients with advanced cHL who had a negative interim PET scan after 2 chemotherapy cycles; patients with a high IPS and high MTV had worse outcomes. “For this subgroup, we need to focus on different approaches than we’ve currently seen to improve their outcomes,” she said.

According to Dr. Advani, these new types of prognostic scores may be used to identify patients for whom a more intensive initial therapy than ABVD would be most useful, while avoiding treatment escalation for those with a good chance of cure with ABVD alone.

Circulating tumor DNA is another emerging tool shown to be a prognostic marker beyond interim PET. Patients who demonstrate higher than a 2 log-fold reduction have been shown to have excellent outcomes.¹⁸ This marker is currently being evaluated in further studies.

Several studies have now shown that vitamin D deficiency (<30 nmol/L) is associated with lower PFS and OS in patients with cHL.¹⁹ “I’ve actually started checking vitamin D levels in all of my patients, and if low, consider replacement therapy” she said.

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References

1. SEER Program (www. SEER. cancer.gov) SEER* STAT data base: Incidence-SEER research Data of registries, Nov 2020 Sub 91975-2018), National cancer Institute, DCCPS, Surveillance Research Program, Released April 2021, based on the November 2020 submission.
2. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med* 2016;374:2419–2429.
3. Straus DJ, Dlugosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol* 2021;8:e410–421.
4. Press OW, Li H, Schoder H, et al. US Intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. *J Clin Oncol* 2016;34:2020–2007.
5. Zinzani PL, Broccoli A, Gioia DM, et al. Interim positron emission tomography response-adapted therapy in advanced-stage Hodgkin lymphoma: final results of the phase II part of the HD0801 study. *J Clin Oncol* 2016;34:1376–1385.
6. Trotman J, Barrington SF. The role of PET in first-line treatment of Hodgkin lymphoma. *Lancet Haematol* 2021;8:e67–79.
7. Stephens DM, Li H, Schoder H, et al. Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma. *Blood* 2019;134:1238–1246.
8. Gallamini A, Tarella C, Viviani S, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 trial. *J Clin Oncol* 2018;36:454–462.
9. Rigacci L, Puccini B, Broccoli A, et al. Clinical characteristics of interim-PET negative patients with a positive end PET from the prospective HD08-01 FIL study. *Ann Hematol* 2020;99:283–291.
10. Gallamini A, Rossi A, Patti C, et al. Consolidation radiotherapy could be safely omitted in advanced Hodgkin lymphoma with large nodal mass in complete metabolic response after ABVD: final analysis of the randomized GITIL/FIL HD0607 trial. *J Clin Oncol* 2020;38:3905–3913.
11. Anderson RA, Remedios R, Kirkwood AA, et al. Determinants of ovarian function after response-adapted therapy in patients with advanced Hodgkin's lymphoma: a secondary analysis of a randomised phase 3 trial. *Lancet Oncol* 2018;19:1328–1337.
12. Demeestere I, Racape J, Dechene J, et al. Gonadal function recovery in patients with advanced Hodgkin lymphoma treated with a PET-adapted regimen: prospective analysis of a randomized phase III trial (AHL2011). *J Clin Oncol* 2021;39:3251–3260.
13. Huntington SF, von Keudell G, Davidoff AJ, et al. Cost-effectiveness analysis of brentuximab vedotin with chemotherapy in newly diagnosed stage III and IV Hodgkin lymphoma [published online October 4, 2018]. *J Clin Oncol*, doi: 10.1200/JCO.18.00122
14. Ramchandren R, Domingo-Domenech E, Rueda A, et al. Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the phase II CheckMate 205 study. *J Clin Oncol* 2019;37:1997–2007.
15. Viviani S, Mazzocchi A, Pavoni C, et al. Early serum TARC reduction predicts prognosis in advanced-stage Hodgkin lymphoma patients treated with a PET-adapted strategy. *Hematol Oncol* 2020;38:501–508.
16. Plattel WJ, Visser L, Diepstra A, et al. Interim thymus and activation regulated chemokine versus interim 18 F-fluorodeoxyglucose positron-emission tomography in classical Hodgkin lymphoma response evaluation. *Br J Haematol* 2020;190:40–44.
17. Gallamini A, Tarella C, Viviani S, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 trial. *J Clin Oncol* 2018;36:454–462.
18. Spina V, Brusca G, Cuccaro A, et al. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. *Blood* 2018;131:2413–2425.
19. Borchmann S, Cirillo M, Goergen H, et al. Pretreatment vitamin D deficiency is associated with impaired progression-free and overall survival in Hodgkin lymphoma. *J Clin Oncol* 2019;37:3528–3537.