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MINI-REVIEW

Optimizing frontline therapy for classical Hodgkin lymphoma: A mini-review of PET-directed chemotherapy, brentuximab-based regimens, and checkpoint inhibitor combinations

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Abstract

Classical Hodgkin lymphoma is a highly curable malignancy, but long-term treatment-related toxicities remain a challenge, especially in young survivors. In recent years, treatment has shifted from traditional doxorubicin, bleomycin, vinblastine, and dacarbazine regimens to novel approaches such as positron emission tomography-guided therapy, brentuximab vedotin-doxorubicin, vinblastine, dacarbazine (AVD), and checkpoint inhibitor combinations such as nivolumab (Nivo)-AVD. This review evaluates these three frontline strategies in terms of efficacy, toxicity, and their potential to personalize treatment and minimize late complications. Drawing from trials such as ECHELON-1, NIVAHL, SWOG S1826, and BREACH, we analyze current evidence, evaluate conflicting data, and propose considerations for tailoring therapy to patient subgroups.

Keywords: Hodgkin lymphoma; ABVD; Brentuximab vedotin; Nivolumab; PET-adapted therapy; Immunotherapy; Frontline treatment; Toxicity

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1. Introduction

Classical Hodgkin lymphoma (cHL) is a category of lymphoid neoplasms composed of an inflammatory microenvironment consisting of malignant Hodgkin/Reed–Sternberg (HRS) cells mixed with an infiltrate of reactive lymphocytes, histiocytes, eosinophils, and plasma cells.[1] HRS cells originate from germinal center B lymphocytes that do not express normal B cell factors and exhibit downregulation of B-cell transcription factors such as PAX5 and OCT2, leading to a dysfunctional immune phenotype.[2] Clinically, cHL presents as painless lymphadenopathy, most commonly in the cervical, supraclavicular, or mediastinal lymph nodes, and is frequently accompanied by B symptoms – fever, drenching night sweats, and significant weight loss – indicative of systemic inflammation.[3] Other symptoms may include pruritus, hepatosplenic involvement, or the discovery of a mediastinal mass, which is particularly common in young adults.[4]

In the United States, data from the SEER program report an annual incidence of approximately 8,500 new cases and a 5-year survival rate exceeding 87%.[5] Although cHL has a high cure rate, especially in adolescents and young adults, survivors often experience late complications such as cardiopulmonary toxicity, infertility, hypothyroidism, and secondary malignancies, particularly in those treated with radiotherapy and alkylating chemotherapy agents.[6,7]

Treatment paradigms have evolved to reduce these toxicities while preserving efficacy. Three regimens are currently under scrutiny for their impact on progression-free survival (PFS), overall survival (OS), and toxicity: Positron emission tomography (PET)-guided doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD), brentuximab vedotin (BV)-doxorubicin, vinblastine, dacarbazine (AVD), and nivolumab (Nivo)-AVD.[1] By analyzing the latest clinical trial data, including the NIVAHL, BREACH, SWOG S1826, and ECHELON-1 studies, this review synthesizes clinical evidence supporting these therapies, examines statistical findings, reconciles differences across key studies, and offers insights into optimizing therapy based on patient characteristics.

2. Methods

A literature search was conducted using PubMed, Embase, and Google Scholar for articles published between 2000 and 2024. Search terms included "Hodgkin lymphoma," "ABVD," "Brentuximab vedotin," "Nivolumab," "PET-adapted therapy," "clinical trials," and "checkpoint inhibitors." Priority was given to randomized controlled trials, prospective cohort studies, and meta-analyses. Only English-language studies with available full texts were included. Reference mining of pivotal trials was also performed to identify additional relevant publications. The data were analyzed and summarized narratively in accordance with PRISMA guidelines for reviews.

3. Mechanisms and rationale for novel frontline agents

3.1. BV

BV is a CD30-directed antibody-drug conjugate that delivers monomethyl auristatin E, a potent antimicrotubule agent, directly into HRS cells. Its incorporation into frontline therapy stems from the ECHELON-1 trial, which showed improved 5-year PFS with BV-AVD over ABVD (82.3% vs. 74.5%).[8] The use of granulocyte-colony stimulating factor (G-CSF) significantly reduced febrile neutropenia rates following a protocol amendment.[9]

3.2. Nivo

Nivo, a PD-1 immune checkpoint inhibitor, enhances T-cell activity by reversing tumor-mediated immunosuppression.[10] The SWOG S1826 trial confirmed Nivo-AVD's superiority over BV-AVD in advanced-stage cHL, with 2-year PFS rates of 92% versus 83%.[11] While immune-related adverse events such as pneumonitis, hepatitis, and hypothyroidism are common, they are typically reversible with prompt management.

3.3. BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD) regimen

BrECADD is a modified escalated BEACOPP regimen used in PET-guided approaches for advanced-stage Hodgkin lymphoma. Early data suggest that it achieves comparable efficacy with reduced gonadotoxicity and hematologic toxicity, making it a promising alternative for patients who require intensive therapy.[12]

4. Therapeutic stratification by disease stage

4.1. Early-stage favorable disease

Early-stage favorable cHL is typically treated with a combination of limited chemotherapy and involved-site radiotherapy (ISRT). The HD10 trial by the German Hodgkin Study Group (GHSG) demonstrated that two cycles of ABVD followed by 20 Gy of ISRT were non-inferior to four cycles with 30 Gy, significantly reducing long-term toxicity without compromising PFS or OS.[13] The UK RAPID trial also investigated PET-adapted therapy, omitting radiotherapy in PET-negative patients after three ABVD cycles. Patients with negative interim PET (PET-2) scans could safely omit radiotherapy, though long-term follow-up from RAPID highlighted slightly higher relapse rates in the radiotherapy-omission group. Results showed slightly inferior but acceptable PFS and equivalent OS, suggesting radiotherapy may be safely omitted in certain low-risk patients.[4]

4.2. Early-stage unfavorable disease

For early-stage unfavorable cHL, the GHSG HD11 and HD14 trials provided key insights. HD11 showed that four cycles of BEACOPP baseline followed by 30 Gy ISRT was more effective in controlling disease than four cycles of ABVD with ISRT. However, due to higher

[1] ABVD is a chemotherapy regimen comprising doxorubicin (Adriamycin), bleomycin sulfate, vinblastine sulfate, and dacarbazine, whereas AVD is composed of doxorubicin (Adriamycin), Vinblastine, and Dacarbazine

Table 1. Comparative analysis of regimens

Regimen	Key trial	2-year PFS (%)	Notable toxicities	Radiotherapy requirement
ABVD (PET-adapted)	RATHL, HD18	~84 – 90	Pulmonary toxicity (bleomycin)	PET-guided; some receive radiotherapy
BV-AVD	ECHELON-1	82	Peripheral neuropathy, febrile neutropenia	Rare
Nivo-AVD	SWOG S1826	94	Immune-related adverse events	Ongoing investigation

Abbreviations: ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine; AVD: Doxorubicin, vinblastine, dacarbazine; BV: Brentuximab vedotin; Nivo: Nivolumab; PET: Positron emission tomography; PFS: Progression-free survival.

toxicity, ABVD remains a common choice, particularly when guided by PET imaging. The HD14 trial used two cycles of escalated BEACOPP followed by two cycles of ABVD and 30 Gy of ISRT, significantly improving tumor control with manageable toxicity. HD11 and HD14 trials explored intensification with BEACOPP variants, leading to better disease control but increased toxicity.[14] The NIVAHL trial offered a PET-adapted, immunotherapy-containing alternative, demonstrating 3-year PFS of 99% and OS of 100% with Nivo-AVD given sequentially or concurrently.[3] Unlike traditional regimens, the NIVAHL trial demonstrated a significant reduction in radiotherapy requirements utilizing Nivo-AVD.

4.3. Advanced-stage cHL

In the ECHELON-1 trial, BV-AVD demonstrated modest improvement in 5-year PFS (82.3%) compared to ABVD (74.5%), with a hazard ratio (HR) of 0.77.[8] Peripheral neuropathy and febrile neutropenia were key toxicities, although febrile neutropenia was significantly reduced with routine G-CSF support. SWOG S1826 replaced BV with Nivo in the AVD backbone and showed significant improvement in 2-year PFS (94% vs. 84%) with an HR of 0.45.[11] BrECADD, a PET-guided variant of BEACOPP, demonstrated excellent control with less toxicity and is under consideration in European treatment protocols.[12]

5. Comparative analysis and clinical implications

Each of the three frontline regimens – PET-adapted ABVD, BV-AVD, and Nivo-AVD – offers unique advantages and trade-offs (Table 1):

- PET-adapted ABVD allows de-escalation in patients with early PET-negativity, limiting exposure to bleomycin and radiotherapy.
- BV-AVD offers improved PFS in advanced-stage disease with reduced pulmonary toxicity but introduces neuropathy and requires growth factor support.
- Nivo-AVD has the most favorable PFS and tolerability, especially in older or frail patients, and may replace traditional regimens over time.

6. Statistical interpretation and conflicting evidence

In the RATHL trial, PET-guided therapy allowed de-escalation by omitting bleomycin in PET-negative patients, improving safety without compromising efficacy.[15] BV-AVD's benefit was primarily driven by early-stage IV patients, while a subgroup analysis showed less benefit in stage III.[9] SWOG S1826 confirmed superior 2-year PFS with Nivo-AVD across all subgroups. Conflicting data from earlier studies questioning checkpoint inhibitors' role in frontline therapy (*e.g.*, CheckMate 205 cohort B) are addressed by S1826's robust randomized data.

7. Cost-effectiveness and patient selection

Nivo-AVD and BV-AVD increase upfront treatment costs but may reduce long-term expenses from fewer relapses and reduced need for salvage therapy or radiotherapy. Comparative cost-effectiveness modeling remains an area requiring further investigations but will be critical in shaping value-based care decisions.

8. Future directions and personalized medicine

Emerging biomarkers (*e.g.*, levels of programmed cell death ligand 1 [PD-L1] and thymus and activation-regulated chemokine) and PET-2 response offer opportunities for personalization. Trials incorporating circulating tumor DNA, cytokine profiling, and machine-learning risk models could further stratify patients to optimize therapy. Reduced-intensity or chemo-free regimens are under evaluation for older or comorbid patients. The RAPID, HD16, and NIVAHL trials provide a foundation for limiting or omitting radiotherapy in patients with early favorable or unfavorable disease achieving PET-negativity. These strategies aim to preserve cure rates while minimizing long-term harm.

9. Conclusion

The evolving treatment landscape of cHL has shifted toward the integration of novel targeted therapies to optimize efficacy while minimizing toxicity. The comparative analysis of PET-directed ABVD, BV-AVD, and Nivo-AVD

highlights the importance of personalized therapeutic strategies based on risk stratification and evolving clinical trial data. cHL remains a curable malignancy, but the emphasis of frontline therapy has shifted from maximizing short-term disease control to optimizing long-term survivorship. Novel frontline regimens – BV-AVD and Nivo-AVD – demonstrate superior PFS and manageable toxicity profiles compared to traditional ABVD. While PET-adapted ABVD remains appropriate for early-stage favorable disease, immunotherapy-based regimens offer compelling advantages in early-unfavorable and advanced-stage diseases. Future research should focus on long-term survival outcomes, biomarker-driven patient selection, and strategies to de-escalate therapy without compromising cure rates. Furthermore, future trials should aim to directly compare Nivo-AVD or BV-AVD with the RATHL protocol in advanced-stage cHL. Immunotherapy-based approaches, as demonstrated by the NIVAHL and SWOG S1826 trials, are ushering in a new era of precision and reduced toxicity management. Integrating long-term outcomes, cost considerations, and personalized markers will refine cHL management.

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Conflict of interest

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Author contributions

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