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Decoding Hodgkin's Lymphoma: Advances in Biology, Diagnostics, and Therapeutic Strategies

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Abstract

Background: Hodgkin's lymphoma (HL) is a malignancy of the lymphatic system characterized by Reed-Sternberg cells. While current treatments have improved outcomes, challenges remain in managing relapsed/refractory disease and mitigating long-term toxicities.

Purpose: This review aims to summarize recent advances in HL biology, diagnostics, and treatment strategies, with a focus on novel therapeutic approaches and emerging research areas.

Main body: Molecular studies have revealed key pathways in HL pathogenesis, including NF-κB and JAK-STAT signaling. Advanced imaging techniques like PET-CT have improved staging and response assessment. Novel therapies, including checkpoint inhibitors, bispecific antibodies, and CAR T-cells, have demonstrated efficacy in relapsed/refractory HL. Targeted agents like BTK and EZH2 inhibitors are being explored. Optimization of conventional therapies continues, with efforts to reduce toxicity while maintaining efficacy. Long-term survivorship issues, particularly cardiovascular complications and secondary malignancies, are receiving increased attention. Fertility preservation strategies have expanded options for young patients. Emerging research areas include epigenetic modifiers, with HDAC inhibitors and EZH2 inhibitors showing promise in early trials. Microbiome studies are exploring associations between gut bacterial composition and HL risk and prognosis. Nanoparticle-based drug delivery systems, including liposomal formulations and polymeric nanoparticles, are being investigated to enhance therapeutic efficacy and reduce toxicity.

Conclusion: Ongoing research in HL is focused on developing more targeted, less toxic therapies and addressing long-term survivorship issues. Integration of novel agents with conventional treatments and personalized approaches based on molecular profiling hold promise for improving outcomes across the spectrum of HL management.

Keywords: Hodgkin's Lymphoma, Immunotherapy, Targeted Therapy, Biomarkers, Precision Oncology

Abbreviations: HL: Hodgkin's Lymphoma; PET-CT: Positron Emission Tomography-Computed Tomography; NF-κB: Nuclear Factor kappa B; JAK-STAT: Janus Kinase-Signal Transducer and Activator of Transcription; BTK: Bruton's Tyrosine Kinase; EZH2: Enhancer of Zeste Homolog 2; CAR T cells: Chimeric Antigen Receptor T cells; ABVD: Adriamycin (doxorubicin), Bleomycin, Vinblastine, Dacarbazine; BEACOPP: Bleomycin, Etoposide, Adriamycin (doxorubicin), Cyclophosphamide, Oncovin (vincristine), Procarbazine, Prednisone; SCT: Stem Cell Transplantation; ASCT: Autologous Stem Cell Transplantation; GVHD: Graft-Versus-Host Disease; RIC: Reduced-Intensity Conditioning; HDAC: Histone Deacetylase; DNMT: DNA Methyltransferase; PRC2: Polycomb Repressive Complex 2; HRS cells: Hodgkin and Reed-Sternberg cells; PD-1: Programmed Cell Death Protein 1; PD-L1: Programmed Death-Ligand 1; IMRT: Intensity-Modulated Radiation Therapy; VMAT: Volumetric Modulated Arc Therapy; ISRT: Involved-Site Radiation Therapy; TAMs: Tumor-Associated Macrophages; BiTEs: Bispecific T cell Engagers; DART: Dual-Affinity Re-Targeting; PI3K: Phosphatidylinositol 3-Kinase; ADCs: Antibody-Drug Conjugates; BV: Brentuximab Vedotin; MMAE: Monomethyl Auristatin E

Introduction

Hodgkin's lymphoma (HL) is a malignancy of the lymphatic system, characterized by the presence of Reed-Sternberg cells. It primarily affects lymph nodes and can spread to other organs. HL is distinct from other lymphomas due to its unique cellular composition and clinical behavior. The disease typically presents with painless lymphadenopathy, often accompanied by systemic symptoms such as fever, night sweats, and weight loss [1]. HL is classified into two main types: classical Hodgkin lymphoma (cHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). cHL is further subdivided into four histological subtypes: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. The etiology of HL involves a complex interplay of genetic, environmental, and immunological factors, with Epstein-Barr virus infection implicated in a subset of cases [2].

The landscape of HL management has evolved significantly over the past few decades, transforming it from a largely fatal disease to one with high cure rates. However, ongoing research and treatment advances remain crucial for several reasons. Firstly, despite overall good outcomes, a subset of patients still experiences refractory or relapsed disease, necessitating more effective salvage strategies. Secondly, conventional treatments, while effective, can lead to significant short-term toxicities and long-term complications, particularly in young patients who constitute a large proportion of HL cases. This underscores the need for less toxic, more targeted therapies. Thirdly, the advent of precision medicine has opened new avenues for personalized treatment approaches, potentially improving outcomes while minimizing adverse effects. Lastly, ongoing research is vital for understanding the complex biology of HL, which can lead to the identification of novel therapeutic targets and biomarkers for better risk stratification. Continued advancements in this field hold the promise of further improving cure rates, reducing treatment-related morbidity, and enhancing the quality of life for HL survivors.

Current Understanding of Hodgkin's Lymphoma Biology

Molecular pathogenesis

The molecular pathogenesis of HL is characterized by complex interactions between neoplastic cells and the surrounding microenvironment. At the core of HL pathogenesis are the Hodgkin and Reed-Sternberg (HRS) cells, which typically comprise less than 1% of the tumor mass. These cells originate from B lymphocytes that have undergone malignant transformation. A hallmark of HRS cells is the constitutive activation of the nuclear factor-κB (NF-κB) pathway, which promotes cell survival and proliferation. This activation is often due to genetic alterations in NF-κB pathway components or upstream signaling molecules [3].

Another critical aspect of HL molecular pathogenesis is the deregulation of the JAK-STAT signaling pathway. Genomic amplifications of the 9p24.1 locus, which contains the JAK2 gene, are frequently observed in HL. This leads to increased JAK2 expression and subsequent STAT activation, promoting cell growth and survival. Additionally, the 9p24.1 amplification enhances the expression of programmed death-ligand 1 (PD-L1) and PD-L2, contributing to immune evasion [4].

The loss of B cell identity is a defining feature of HRS cells. This is partly due to the downregulation of B cell-specific transcription factors such as PAX5, OCT2, and BOB1. The absence of these factors results in the loss of B cell receptor expression, a characteristic feature of HRS cells. Despite this loss of B cell phenotype, HRS cells often express markers of other hematopoietic lineages, contributing to their unique immunophenotype [1].

Role of the tumor microenvironment

The tumor microenvironment plays a crucial role in the pathogenesis and progression of HL. Unlike many other malignancies, the bulk of the HL tumor mass consists of non-malignant inflammatory cells, including T cells, B cells, macrophages, eosinophils, and plasma cells. This inflammatory infiltrate is actively recruited and maintained by the HRS cells through the secretion of various cytokines and chemokines.

T cells, particularly CD4+ T helper cells, are abundant in the HL microenvironment and contribute to the survival and proliferation of HRS cells. These T cells often exhibit a T helper 2 (Th2) or T regulatory (Treg) phenotype, which can suppress anti-tumor immune responses. HRS cells attract these T cells through the secretion of chemokines such as CCL5, CCL17, and CCL22 [5].

Macrophages are another important component of the HL microenvironment. Tumor-associated macrophages (TAMs) can promote tumor growth by secreting pro-angiogenic factors and immunosuppressive cytokines. The presence of high numbers of CD68+ macrophages in HL tumors has been associated with poor prognosis, highlighting their clinical significance [6].

The HL microenvironment is also characterized by an abundance of extracellular matrix components, including collagen and fibronectin. These components can provide survival signals to HRS cells and contribute to the characteristic nodular sclerosis observed in some HL subtypes. Additionally, the extracellular matrix can act as a physical barrier, limiting the infiltration of cytotoxic immune cells [7].

Angiogenesis plays a crucial role in the HL microenvironment. HRS cells secrete pro-angiogenic factors such as vascular endothelial growth factor (VEGF), which promotes the formation of new blood vessels. This increased vasculature not only supports tumor growth but also facilitates the recruitment of inflammatory cells to the tumor site [8].

Recent genomic and epigenomic insights

Recent advances in genomic and epigenomic profiling techniques have provided new insights into the molecular landscape of HL. Whole-exome and whole-genome sequencing studies have revealed recurrent genetic alterations in HL, including mutations in genes involved in NF-κB signaling (e.g., TNFAIP3, NFKBIE), JAK-STAT signaling (e.g., STAT6), and epigenetic regulation (e.g., KMT2D, CREBBP) [9].

One of the most significant recent findings is the identification of recurrent mutations in the PTPN1 gene, which encodes the protein tyrosine phosphatase SHP-1. These mutations lead to increased JAK-STAT signaling and contribute to the growth and survival of HRS cells. This discovery has not only enhanced our understanding of HL pathogenesis but also highlighted potential new therapeutic targets [10].

Epigenomic studies have revealed extensive DNA methylation changes in HRS cells compared to normal B cells. Hypermethylation of tumor suppressor genes and genes involved in B cell differentiation contributes to the loss of B cell identity and promotes lymphomagenesis. Conversely, hypomethylation of certain loci leads to the aberrant expression of genes that are typically silenced in B cells.

Recent research has also focused on the role of non-coding RNAs in HL pathogenesis. MicroRNAs (miRNAs) have emerged as important regulators of gene expression in HL. For example, the miR-155 is frequently upregulated in HL and contributes to the activation of the PI3K-AKT pathway. Long non-coding RNAs (lncRNAs) are also being investigated for their potential roles in HL biology, with some lncRNAs showing altered expression patterns in HRS cells [11].

Advanced Diagnostic Techniques

Improved imaging modalities (e.g., PET-CT, whole-body MRI)

The landscape of HL diagnosis and staging has been revolutionized by advancements in imaging modalities. Positron Emission Tomography-Computed Tomography (PET-CT) has emerged as the gold standard for initial staging and response assessment in HL. This hybrid imaging technique combines the anatomical precision of CT with the metabolic information provided by PET, offering a comprehensive evaluation of disease extent and activity [12].

PET-CT utilizes 18F-fluorodeoxyglucose (FDG), a glucose analog that accumulates in metabolically active tissues, including lymphoma cells. The standardized uptake value (SUV) of FDG serves as a quantitative measure of metabolic activity, allowing for objective assessment of treatment response. The Deauville criteria, a five-point scale based on FDG uptake, has been widely adopted for response evaluation in HL. This standardized approach has significantly improved the accuracy of interim and end-of-treatment assessments, enabling more personalized treatment strategies [13].

Whole-body Magnetic Resonance Imaging (WB-MRI) has emerged as a promising radiation-free alternative for lymphoma staging, particularly in pediatric and young adult populations. WB-MRI offers excellent soft tissue contrast and can detect bone marrow involvement with high sensitivity. Diffusion-weighted imaging (DWI), a functional MRI technique, provides information on tissue cellularity and has shown utility in differentiating between active and treated lesions [14].

The integration of PET with MRI (PET-MRI) represents the cutting edge of hybrid imaging. This modality combines the metabolic information of PET with the superior soft tissue contrast of MRI, potentially offering advantages in certain anatomical regions such as the central nervous system and bone marrow. While still in the early stages of clinical implementation for lymphoma, PET-MRI shows promise for comprehensive one-stop imaging in HL management.

Liquid biopsy and circulating tumor DNA analysis

Liquid biopsy has emerged as a non-invasive diagnostic tool with significant potential in HL management. This technique involves the analysis of circulating tumor DNA (ctDNA) in peripheral blood, offering a real-time snapshot of tumor genetics without the need for invasive tissue biopsies [15].

In HL, ctDNA analysis has shown promise in several areas of disease management. Firstly, it can serve as a diagnostic tool, particularly in cases where tissue biopsy is challenging or contraindicated. The detection of characteristic genetic alterations associated with HL, such as 9p24.1 amplifications or PTPN1 mutations, in ctDNA can support the diagnosis of HL [16].

Secondly, ctDNA analysis has demonstrated utility in disease monitoring and early detection of relapse. Studies have shown that changes in ctDNA levels often precede clinical or radiological evidence of disease progression. This early warning system could potentially allow for more timely intervention and improved outcomes.

The quantification of ctDNA has also shown promise as a prognostic marker. Higher levels of ctDNA at diagnosis or during treatment have been associated with poorer outcomes in some studies, suggesting its potential as a biomarker for risk stratification [16].

Artificial intelligence in pathology and radiology

Artificial intelligence (AI) is rapidly transforming the landscape of HL diagnosis and management, with applications in both pathology and radiology as shown in (**Table 1**). In pathology, AI algorithms, particularly deep learning models, are being developed to assist in the analysis of histopathological slides.

Table 1. Advanced diagnostic techniques.

Diagnostic Technique	Description	Key Features	Clinical Applications	Advantages	Limitations	Current Status
PET-CT	Hybrid imaging combining metabolic (PET) and anatomical (CT) information	Uses FDG to detect metabolically active tissues	Initial staging, response assessment, end-of-treatment evaluation	High sensitivity, standardized evaluation (Deauville criteria)	Radiation exposure, false positives due to inflammation	Gold standard for HL imaging
Whole-body MRI	Radiation-free imaging technique with high soft tissue contrast	Includes diffusion-weighted imaging (DWI)	Staging, particularly in pediatric/young adult populations	No radiation, superior bone marrow assessment	Limited availability, longer scan times	Emerging alternative to PET-CT
PET-MRI	Combines PET metabolic imaging with MRI soft tissue contrast	Simultaneous acquisition of PET and MRI data	Comprehensive staging, particularly for CNS involvement	Reduced radiation compared to PET-CT, superior soft tissue contrast	Limited availability, high cost	Early clinical implementation
Liquid Biopsy (ctDNA analysis)	Detection of circulating tumor DNA in peripheral blood	Analyzes characteristic genetic alterations (e.g., 9p24.1 amplifications)	Diagnosis, disease monitoring, early relapse detection	Non-invasive, real-time assessment of tumor genetics	Lower sensitivity in low tumor burden, standardization needed	Emerging technique, active research
AI-assisted Pathology	Machine learning algorithms for histopathological analysis	Automated detection and classification of HRS cells	Diagnosis, subtype classification	Increased efficiency, potential for standardization	Requires large annotated datasets, validation needed	Early clinical implementation
AI-assisted Radiology	Machine learning for medical image analysis	Radiomic feature extraction and analysis	Predicting treatment response, outcome	Potential for novel imaging biomarkers	Requires large datasets, standardization challenges	Active research area
Multiplex Immunohistochemistry	Simultaneous detection of multiple proteins on a single tissue section	Characterizes tumor microenvironment components	Detailed analysis of immune cell infiltrates, prognostication	Comprehensive tissue analysis, spatial information	Technical complexity, standardization challenges	Emerging research tool
Single-cell RNA Sequencing	High-resolution transcriptomic profiling at single-cell level	Reveals cellular heterogeneity within HL samples	Identifying distinct cell populations, potential therapeutic targets	Unprecedented resolution of cellular composition	High cost, complex data analysis	Cutting-edge research tool

FDG: Fluorodeoxyglucose; HRS: Hodgkin and Reed-Sternberg; CNS: Central Nervous System; AI: Artificial Intelligence

AI-powered image analysis tools can aid in the detection and classification of Hodgkin and Reed-Sternberg (HRS) cells, the hallmark cells of HL. These systems can rapidly process large numbers of digital pathology images, potentially improving diagnostic accuracy and efficiency. Machine learning algorithms have shown promise in distinguishing between HL subtypes and identifying subtle morphological features that may have prognostic significance [17].

Furthermore, AI techniques are being applied to multiplex immunohistochemistry data, allowing for more comprehensive characterization of the tumor microenvironment. These tools can quantify the spatial relationships between different cell types, providing insights into the complex interactions between HRS cells and the surrounding immune infiltrate [18].

AI techniques are also being applied to radiomics, the high-throughput extraction of quantitative features from medical images. Radiomic features, when combined with clinical and genomic data, have shown potential in predicting treatment response and outcome in HL. AI algorithms can analyze these complex, multidimensional datasets to identify novel imaging biomarkers and develop predictive models [19].

Risk Stratification and Personalized Treatment Approaches

Prognostic biomarkers

The field of HL has witnessed significant advancements in the identification and validation of prognostic biomarkers, enabling more precise risk stratification and tailored treatment approaches. These biomarkers encompass a diverse range of molecular, cellular, and clinical parameters that collectively provide a comprehensive assessment of disease behavior and potential treatment outcomes [16].

Serum biomarkers have emerged as valuable prognostic tools in HL management. Elevated levels of soluble CD30 (sCD30), a member of the tumor necrosis factor receptor superfamily, have been associated with adverse outcomes in HL patients. sCD30 levels correlate with tumor burden and serve as an indicator of treatment response. Similarly, serum thymus and activation-regulated chemokine (TARC/CCL17) has gained attention as a biomarker for disease activity and treatment monitoring. TARC levels typically decrease with successful therapy and can predict early relapse when elevated post-treatment [20].

The tumor microenvironment plays a crucial role in HL pathogenesis, and biomarkers derived from this complex milieu have shown prognostic value. Immunohistochemical assessment of tumor-associated macrophages (TAMs) using CD68 or CD163 staining has emerged as a powerful prognostic tool. High TAM infiltration is associated with inferior outcomes and may identify patients who could benefit from intensified therapy or novel targeted approaches [21].

Gene expression profiling

Gene expression profiling (GEP) has emerged as a powerful tool for molecular classification and risk stratification in HL. High-throughput technologies such as microarrays and RNA sequencing have enabled comprehensive analysis of the transcriptome, revealing distinct molecular subtypes with prognostic implications [22].

Studies utilizing GEP have identified gene signatures associated with treatment response and outcome in HL. A notable example is the 23-gene predictor of treatment failure, which includes genes involved in macrophage function, angiogenesis, and apoptosis regulation. This signature has shown promise in identifying patients at high risk of primary treatment failure who may benefit from alternative therapeutic strategies [23].

Gene expression analysis of the tumor microenvironment has provided insights into the complex interactions between malignant Hodgkin and Reed-Sternberg (HRS) cells and surrounding immune cells. Signatures reflecting T cell exhaustion or regulatory T cell infiltration have been associated with poor prognosis, highlighting the importance of the immune microenvironment in disease progression [24].

Recent advancements in single-cell RNA sequencing technologies have enabled more granular analysis of gene expression patterns at the cellular level. These approaches have revealed heterogeneity within HRS cells and identified distinct subpopulations with varying gene expression profiles. Such insights may lead to more refined prognostic models and targeted therapeutic approaches [25].

Metabolomic and proteomic markers

Metabolomic studies in HL have identified distinct metabolic signatures associated with disease status and prognosis. Alterations in energy metabolism, particularly in glucose utilization and lipid metabolism, have been observed in HL patients. Specific metabolites, such as 2-hydroxyglutarate and kynurenine, have shown promise as potential biomarkers for disease activity and treatment response [26].

Serum metabolomic profiling has revealed patterns that can distinguish HL patients from healthy individuals and potentially predict treatment outcomes. Metabolites involved in amino acid metabolism, fatty acid oxidation, and nucleotide synthesis have been implicated in these predictive models. Such metabolic signatures may provide complementary information to existing biomarkers and contribute to more accurate risk stratification [27].

Proteomic analysis of HL tissues and serum samples has identified protein signatures associated with disease progression and treatment response. Mass spectrometry-based approaches have enabled the quantification of

thousands of proteins, revealing alterations in pathways related to immune regulation, cell survival, and angiogenesis [28].

Serum proteomics has shown potential for non-invasive monitoring of HL. Studies have identified panels of serum proteins that can differentiate HL patients from healthy controls and potentially predict treatment outcomes. Proteins involved in inflammation, immune response, and extracellular matrix remodeling have been implicated in these predictive signatures [29].

Novel Therapeutic Strategies

Immunotherapy

Checkpoint inhibitors (e.g., PD-1, PD-L1 inhibitors): Checkpoint inhibitors have revolutionized the treatment landscape of HL, particularly in relapsed or refractory disease. These agents target the programmed cell death protein 1 (PD-1) pathway, which is frequently exploited by HL cells to evade immune surveillance. The genetic amplification of 9p24.1, a common feature in HL, leads to overexpression of PD-L1 and PD-L2, making HL particularly susceptible to PD-1 blockade [30].

Anti-PD-1 monoclonal antibodies, such as nivolumab and pembrolizumab, have demonstrated remarkable efficacy in relapsed/refractory HL. These agents have shown overall response rates exceeding 65% in heavily pretreated patients, with durable responses observed in a significant proportion of cases. The success of these agents has led to their approval for use in relapsed/refractory HL and ongoing investigations in earlier lines of therapy [31].

Recent studies have explored the potential of PD-L1 inhibitors in HL. While less extensively studied than PD-1 inhibitors, agents targeting PD-L1 have shown promising results in early-phase trials. The dual targeting of PD-1 and PD-L1 is an area of active investigation, aiming to enhance the efficacy of checkpoint blockade in HL [32].

Bispecific antibodies: Bispecific antibodies represent an innovative approach to harnessing the immune system against HL as shown in **Table 2**. These engineered molecules simultaneously bind to tumor-associated antigens on HL cells and to effector T cells, facilitating targeted immune activation against the malignant cells [33].

CD30-directed bispecific antibodies have shown particular promise in HL. These agents typically target CD30 on HL cells

Table 2. Novel therapeutic approaches.

Therapeutic Approach	Mechanism of Action	Key Agents	Detailed Clinical Efficacy	Notable Adverse Effects	Current Status
Checkpoint Inhibitors	Block PD-1/PD-L1 interaction, enhancing T cell anti-tumor activity	Nivolumab, Pembrolizumab	ORR >65% in r/r HL. Studies show durable responses, with complete response rates of 16-22% and median progression-free survival of 14-18 months.	Immune-related adverse events (e.g., pneumonitis, colitis, thyroid dysfunction)	Approved for r/r HL
Bispecific Antibodies	Simultaneously bind CD30 on HL cells and CD3 on T cells	Various CD30/CD3 bispecifics (e.g., AFM13)	Promising early-phase results. Phase I trials of AFM13 showed ORR of 11.5% in heavily pretreated r/r HL patients. Combination trials ongoing.	Cytokine release syndrome, neurotoxicity	Phase I/II trials
BTK Inhibitors	Inhibit B-cell receptor signaling and NF-κB pathway	Ibrutinib, Next-generation BTK inhibitors	Modest single-agent activity. Phase I/II trials of ibrutinib showed ORR of 9.4% in r/r HL. Combination strategies being explored.	Bleeding risk, atrial fibrillation	Phase II trials
EZH2 Inhibitors	Target epigenetic regulation via histone methyltransferase inhibition	Tazemetostat	ORR >50% in r/r HL. Phase II study of tazemetostat showed ORR of 56% with median duration of response of 8.9 months.	Thrombocytopenia, neutropenia	Phase II trials
PI3K Inhibitors	Block PI3K signaling pathway	Various delta isoform inhibitors	ORR 20-40% in r/r HL. Phase II study of copanlisib showed ORR of 40% with median progression-free survival of 5.7 months.	Hepatotoxicity, colitis	Phase II trials

Antibody-Drug Conjugates	Targeted delivery of cytotoxic agents to CD30+ cells	Brentuximab vedotin	ORR >70% in r/r HL. Pivotal phase II trial showed ORR of 75% with complete response rate of 34%. Five-year progression-free survival of 22%.	Peripheral neuropathy, neutropenia	Approved for r/r HL and frontline use
CAR T-cell Therapy	Genetically modified T cells targeting CD30	Various CD30-directed CAR T-cells	Early promising results. Phase I trials show ORR of 72% with complete response rate of 59% in heavily pretreated r/r HL patients.	Cytokine release syndrome, neurotoxicity	Phase I/II trials
Epigenetic Modifiers (non-EZH2)	Alter gene expression via histone modifications	HDAC inhibitors (e.g., Panobinostat)	Under investigation. Phase II study of panobinostat showed ORR of 27% in r/r HL patients.	Fatigue, thrombocytopenia	Phase I/II trials
Nanoparticle Drug Delivery	Enhanced drug delivery and tumor targeting	Liposomal doxorubicin, Polymeric nanoparticles	Preclinical/early clinical stage. Limited efficacy data available in HL. Liposomal doxorubicin showed some activity in combination regimens.	Dependent on payload	Preclinical/Phase I

ORR: Overall Response Rate; r/r HL: Relapsed/refractory Hodgkin's Lymphoma; BTK: Bruton's Tyrosine Kinase; EZH2: Enhancer of Zeste Homolog 2; PI3K: Phosphatidylinositol 3-kinase; HDAC: Histone Deacetylase

and CD3 on T cells, promoting T cell-mediated cytotoxicity against CD30-positive tumor cells. Early-phase clinical trials have demonstrated encouraging response rates in relapsed/refractory HL patients, including those who have progressed after checkpoint inhibitor therapy [34].

Recent advancements in antibody engineering have led to the development of next-generation bispecific formats with improved stability, half-life, and efficacy. These include bispecific T cell engagers (BiTEs) and dual-affinity re-targeting (DART) molecules, which are being evaluated in ongoing clinical trials for HL [35].

Targeted therapies

BTK inhibitors: Bruton's tyrosine kinase (BTK) inhibitors have emerged as a promising class of targeted therapies in HL. While BTK is typically associated with B cell receptor signaling, its role in the survival of Hodgkin and Reed-Sternberg (HRS) cells has been increasingly recognized. First-generation BTK inhibitors, such as ibrutinib, have shown modest single-agent activity in relapsed/refractory HL. However, next-generation, more selective BTK inhibitors are being evaluated with the aim of improving efficacy and reducing off-target effects [36].

EZH2 inhibitors: Enhancer of zeste homolog 2 (EZH2) inhibitors represent a novel class of epigenetic modifiers with potential efficacy in HL. EZH2 is a histone methyltransferase that plays a crucial role in transcriptional repression and has been implicated in HL pathogenesis.

Early-phase clinical trials of EZH2 inhibitors in relapsed/refractory HL have demonstrated promising results, with overall response rates exceeding 50% in heavily pretreated patients. These agents appear to be well-tolerated, with a favorable safety profile compared to conventional chemotherapy [37].

PI3K inhibitors: Phosphatidylinositol 3-kinase (PI3K) inhibitors have shown promise in the treatment of HL, particularly targeting the delta isoform of PI3K, which is critical for B-cell signaling and survival. While HL cells typically lack B-cell receptor expression, PI3K signaling remains important for their growth and survival. Clinical trials of PI3K delta inhibitors in relapsed/refractory HL have demonstrated modest single-agent activity, with overall response rates ranging from 20-40%. These agents have shown particular efficacy in nodular lymphocyte-predominant HL, a rare subtype with distinct biology [38].

Antibody-drug conjugates (e.g., Brentuximab vedotin)

Antibody-drug conjugates (ADCs) have revolutionized the treatment of HL, with brentuximab vedotin (BV) serving as a paradigm for this class of agents. BV consists of an anti-CD30 monoclonal antibody linked to the potent microtubule-disrupting agent monomethyl auristatin E (MMAE) [39].

The success of BV in relapsed/refractory HL, with response rates exceeding 70%, has led to its incorporation into earlier lines of therapy. BV has shown significant benefit when combined with chemotherapy in the frontline treatment of advanced-stage HL, leading to improved progression-free survival compared to conventional chemotherapy alone [40].

Optimizing Conventional Therapies

Chemotherapy regimens (e.g., ABVD, escalated BEACOPP)

The optimization of conventional chemotherapy regimens remains a crucial aspect of HL management, with ongoing efforts to enhance efficacy while minimizing toxicity. The two primary chemotherapy backbones in HL treatment are ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) [41].

ABVD has long been the standard of care for many patients with HL, offering a favorable balance of efficacy and toxicity. Recent refinements in ABVD administration have focused on reducing long-term toxicities while maintaining efficacy. The omission of bleomycin after achieving negative interim PET (positron emission tomography) results has become a widely adopted strategy, significantly reducing the risk of pulmonary toxicity without compromising treatment outcomes [42].

Escalated BEACOPP, while associated with higher toxicity, has demonstrated superior efficacy in advanced-stage HL. Recent studies have explored de-escalation strategies for patients achieving early metabolic response, aiming to maintain high cure rates while reducing treatment-related morbidity. These approaches include switching to ABVD or omitting bleomycin and vincristine in later cycles based on interim PET results [43].

Radiation therapy techniques

Radiation therapy (RT) remains an important component of HL treatment, particularly in early-stage disease. However, the role and optimal application of RT have evolved significantly in recent years, driven by efforts to minimize long-term toxicities while maintaining excellent disease control.

Advanced RT techniques have revolutionized the field, allowing for more precise and targeted treatment delivery. Intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) enable highly conformal dose distribution, sparing adjacent normal tissues. These techniques have shown particular benefit in reducing cardiac and pulmonary exposure in mediastinal HL [44].

Proton therapy has emerged as a promising modality in HL, offering superior dose distribution compared to photon-based techniques. The unique physical properties of protons allow for a sharp dose fall-off beyond the target volume, potentially reducing the integral dose to surrounding tissues. While long-term data are still maturing, early results suggest a favorable toxicity profile, particularly for young patients and those with mediastinal involvement [45].

The concept of involved-site radiation therapy (ISRT) has largely replaced the older involved-field approach [46]. ISRT further refines the treatment volume, targeting only the initially involved lymph node regions with a margin. This approach, combined with advanced delivery techniques, has allowed for significant reductions in treatment volumes and doses without compromising disease control [47].

Stem cell transplantation advances

Stem cell transplantation (SCT) remains a cornerstone in the management of relapsed or refractory HL, with ongoing advancements aimed at improving outcomes and reducing complications. Autologous SCT (ASCT) continues to be the standard of care for chemosensitive relapsed HL. Recent efforts have focused on optimizing pre-transplant salvage regimens and incorporating novel agents into the transplant paradigm. The use of PET-guided strategies to assess chemosensitivity before ASCT has improved patient selection and outcomes [48].

The integration of post-transplant consolidation therapy has shown promise in reducing relapse rates after ASCT. Brentuximab vedotin maintenance therapy post-ASCT has demonstrated significant improvements in progression-free survival, particularly in high-risk patients [49].

Novel conditioning regimens for ASCT are being explored to enhance anti-lymphoma efficacy while reducing toxicity. The incorporation of targeted agents, such as bendamustine or novel antibody-drug conjugates, into conditioning protocols is under investigation.

Allogeneic SCT, while associated with higher treatment-related mortality, offers the potential for long-term disease control in selected patients with relapsed/refractory HL. Recent advances in allogeneic SCT have focused on reducing transplant-related complications and improving graft-versus-lymphoma effects [50].

Reduced-intensity conditioning (RIC) regimens have expanded the applicability of allogeneic SCT to older patients and those with comorbidities. These approaches rely more heavily on immunologic graft-versus-lymphoma effects rather than high-dose chemotherapy for disease control [51]. Haploidentical transplantation has emerged as a viable alternative for patients lacking HLA-matched donors. The use of post-transplant cyclophosphamide for graft-versus-host disease (GVHD) prophylaxis has significantly improved outcomes in haploidentical SCT, making it a competitive option compared to matched unrelated donor transplants [52].

Emerging Research Areas

Epigenetic modifiers

Epigenetic dysregulation has emerged as a critical factor in the pathogenesis of HL, prompting intense investigation into epigenetic modifiers as potential therapeutic targets [13].

Recent advances in epigenomic profiling technologies have revealed distinct epigenetic signatures in HL, characterized by aberrant DNA methylation patterns and histone modifications [53,54].

Histone deacetylase (HDAC) inhibitors represent a class of epigenetic modifiers that have shown promise in HL. These agents promote histone acetylation, leading to chromatin relaxation and reactivation of silenced tumor suppressor genes. Early-phase clinical trials of HDAC inhibitors, both as monotherapy and in combination with standard treatments, have demonstrated encouraging results in relapsed/refractory HL patients [55].

Enhancer of zeste homolog 2 (EZH2) inhibitors have garnered significant attention in HL research. EZH2, a histone methyltransferase and core component of the polycomb repressive complex 2 (PRC2), is frequently overexpressed in HL. Selective EZH2 inhibitors have shown remarkable efficacy in preclinical models and early clinical trials, particularly in cases with EZH2 activating mutations or overexpression [56].

DNA methyltransferase (DNMT) inhibitors are being explored for their potential to reverse aberrant DNA methylation patterns in HL. While these agents have shown efficacy in other hematological malignancies, their role in HL is still being defined. Ongoing research is focused on identifying specific methylation signatures that may predict response to DNMT inhibition [57-59].

Microbiome studies in Hodgkin's lymphoma

The role of the human microbiome in cancer development and treatment response has gained increasing attention, with recent studies exploring its potential implications in Hodgkin's lymphoma. The complex interplay between the host immune system and the microbiome is of particular interest in HL, given the disease's unique immunological features [60].

Gut microbiome composition has been associated with HL risk and prognosis in preliminary studies. Specific bacterial taxa have been found to be enriched or depleted in HL patients compared to healthy controls, suggesting potential microbial signatures associated with the disease. Ongoing research aims to elucidate whether these alterations are a cause or consequence of HL development and progression [61-64].

Nanoparticle-based drug delivery systems

Nanoparticle-based drug delivery systems represent a cutting-edge approach to improving therapeutic efficacy and reducing toxicity in HL treatment as shown in (**Table 3)**. These nanoscale carriers offer the potential for enhanced drug solubility, targeted delivery to tumor sites, and improved pharmacokinetic profiles [65].

Liposomal formulations of conventional chemotherapeutic agents have shown promise in HL. Nanoparticle encapsulation of drugs such as doxorubicin has demonstrated reduced cardiotoxicity while maintaining anti-tumor efficacy. Ongoing research is focused on optimizing liposome composition and surface modifications to enhance tumor targeting and drug release kinetics [66-70].

Polymeric nanoparticles are being investigated as versatile

Table 3. Emerging research areas in Hodgkin's lymphoma.

Research Area	Key Concepts	Potential Targets/ Approaches	Preclinical Findings	Clinical Progress	Challenges	Future Directions
Epigenetic Modifiers	Targeting aberrant epigenetic regulation in HL	HDAC inhibitors, EZH2 inhibitors, DNMT inhibitors	Reversal of silenced tumor suppressor genes, anti-proliferative effects	Phase I/II trials of HDAC and EZH2 inhibitors showing promise	Identifying predictive biomarkers, optimizing combination strategies	Exploring synergies with immunotherapy, developing more selective inhibitors
Microbiome Studies	Investigating gut microbiome influence on HL pathogenesis and treatment	Specific bacterial taxa associated with HL risk/ prognosis	Alterations in microbial diversity in HL patients, potential immunomodulatory effects	Preliminary studies showing associations between microbiome composition and HL outcomes	Establishing causality, standardizing microbiome analysis methods	Microbiome-based risk stratification, therapeutic microbiome modulation
Nanoparticle-based Drug Delivery	Enhancing drug efficacy and reducing toxicity through targeted delivery	Liposomal formulations, polymeric nanoparticles, gold nanoparticles	Improved pharmacokinetics, enhanced tumor targeting in preclinical models	Early-phase trials of liposomal chemotherapeutics	Optimizing nanoparticle design for tumor penetration, scaling up production	Developing "smart" nanoparticles responsive to tumor microenvironment

Tumor Microenvironment Modulation	Targeting non-malignant cells supporting HL growth	TAM-directed therapies, angiogenesis inhibitors, ECM modulators	Disruption of pro-tumor microenvironment in animal models	Preclinical stage, some ECM modulators in early clinical testing	Balancing microenvironment modulation with anti-tumor immunity	Combining with immunotherapies, developing biomarkers of microenvironment state
Novel Immunotherapy Approaches	Enhancing anti-tumor immune responses	Bi-specific T cell engagers, CAR NK cells, vaccine approaches	Potent anti-tumor activity in preclinical models	Early-phase trials of bi-specific antibodies and CAR therapies	Managing toxicities, improving persistence of engineered cells	Developing "off-the-shelf" cellular therapies, exploring combination immunotherapies
Liquid Biopsy Advancements	Non-invasive disease monitoring and prognostication	ctDNA analysis, circulating tumor cells, exosomes	Correlation of ctDNA levels with disease burden and treatment response	Validation studies for ctDNA as biomarker of minimal residual disease	Standardizing analysis methods, improving sensitivity for low disease burden	Integrating liquid biopsy into routine clinical practice, developing multi-analyte liquid biopsy panels
Precision Medicine Approaches	Tailoring therapy based on molecular profiling	NGS-based prognostic models, pharmacogenomics	Identification of novel prognostic markers and therapeutic targets	Implementation of NGS in clinical trials for patient stratification	Integrating complex molecular data into clinical decision-making	Developing AI-assisted treatment algorithms, conducting basket trials based on molecular features

HDAC: Histone Deacetylase; EZH2: Enhancer of Zeste Homolog 2; DNMT: DNA Methyltransferase; TAM: Tumor-Associated Macrophages; ECM: Extracellular Matrix; CAR: Chimeric Antigen Receptor; NK: Natural Killer; ctDNA: Circulating Tumor DNA; NGS: Next-Generation Sequencing; AI: Artificial Intelligence

carriers for a range of therapeutic agents in HL. These biodegradable nanocarriers can be engineered to encapsulate both hydrophilic and hydrophobic drugs, as well as nucleic acid-based therapeutics. Surface functionalization with targeting ligands, such as CD30 antibodies, is being explored to enhance specificity for HL cells [71].

Gold nanoparticles have garnered interest in HL research for their unique optical properties and potential for photothermal therapy. These nanoparticles can be conjugated with targeting antibodies and therapeutic agents, offering a multifunctional platform for combined imaging and therapy. Preclinical studies have demonstrated enhanced radiosensitization effects when gold nanoparticles are combined with radiation therapy in HL models [72].

Conclusions

Recent advances in HL research have significantly enhanced our understanding of disease biology and expanded therapeutic options. The integration of novel targeted therapies, particularly checkpoint inhibitors and antibody-drug conjugates, has markedly improved outcomes for relapsed/refractory patients. Refinements in conventional therapies, including PET-guided treatment de-escalation and advanced radiation techniques, have optimized the balance between efficacy and toxicity. Emerging research in epigenetic modifiers, microbiome studies, and nanoparticle-based drug delivery systems shows promise for further therapeutic innovations. These developments collectively represent a paradigm shift towards more personalized and less toxic treatment strategies. However, challenges remain, including the management of treatment-resistant disease, mitigation of long-term complications, and the need for biomarkers to guide therapy selection. Furthermore, while novel therapies have shown impressive response rates, long-term follow-up data are still maturing, and their optimal integration into treatment algorithms requires further study.

Recommendations

Future research in HL should prioritize several key areas to address current limitations and capitalize on emerging opportunities. Firstly, large-scale genomic and epigenomic profiling studies are needed to identify novel therapeutic targets and develop more precise prognostic models. Secondly, prospective trials should focus on optimizing combination strategies incorporating novel agents with conventional therapies, aiming to improve cure rates while minimizing toxicity. Thirdly, long-term follow-up studies are crucial to fully assess the efficacy and safety profiles of new treatments, particularly in terms of late effects and quality of life. Fourthly, increased effort should be directed towards understanding and leveraging the tumor microenvironment and host immune system, potentially leading to more effective immunotherapeutic approaches. Finally, translational research should aim to develop and validate biomarkers for treatment response and toxicity, enabling truly personalized treatment strategies.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data is available, and sharing is available as well as publication.

Competing interests

The authors hereby declare that they have no competing interests.

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Authors' contributions

The author completed the study protocol and was the primary organizer of data collection and the manuscript's draft and revision process. Corresponding author wrote the article and ensured its accuracy.

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