RES MEDICA
Journal of the Royal Medical Society
Res Medica 2015, Volume 23, Issue 1

SPECIAL ARTICLE

Classical Hodgkin's Lymphoma: Pathogenesis and Future Treatment Directions

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ABSTRACT

Classical Hodgkin Lymphoma is a germinal center B cell malignancy. Over the past 40 years, through greater understanding of disease pathogenesis, advancements in treatment have lead to greater than 80% long-term survival rates after standard first line therapy.[1] Currently, first-line management of the disease varies, most commonly involving the use of a standard chemotherapy regime (i.e. ABVD or BEACOPP), with or without the use of additional chemotherapies or involved-field radiation therapy.[2] Treatment selection is influenced by disease staging at diagnosis and the need to maintain therapeutic efficacy, whilst minimising the risk of late and potentially fatal therapy-associated side effects.[2] Consequently, higher than acceptable drug-associated toxicities and patient relapse represent the future challenges of this disease. Novel therapies, targeting the aberrant signalling pathways and phenotypic features of the malignant cell pool, and its associated inflammatory infiltrate, are the future direction of disease management. Currently, combination therapies targeting the PI3K/Akt/mTOR pathway and transcription modulation have shown the greatest clinical efficacy in improving survival outcomes in previously heavily treated cHL patients, with minimal side effects. Whilst these therapies do not yet achieve the clinical efficacy of first line therapies, preliminary stage I and II trials have demonstrated a reduction in drug associated toxicities and side effects relative to existing treatments for relapse. This paper will investigate current understanding of the pathogenesis of cHL, and how this has shaped the targets of novel therapies for the disease.

ISSN: 2051-7580 (Online) ISBN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, 2015, 23(1):48-57.
doi:10.2218/resmedica.v23i1.1250

Introduction

Adaptive immunity consists of a population of lymphocytes, which confer highly specific and long lasting immunity against pathogenic agents.[4] The immune response generated can be classified as either humoral or cell mediated, and serves to eliminate pathogens from the body.[4] When the normal processes that drive the development, differentiation or activation of these lymphocytes become distorted, pathologies of the immune system may result.

Approximately 95% of all lymphomas are of B cell origin. This includes Hodgkin lymphoma (HL), which accounts for 0.6% of newly diagnosed cancer cases each year and is attributed to 0.5% of all deaths due to cancer.[3,5,6] The disease is associated with characteristic B symptoms, which include night sweats, fever (>38°C), and weight loss (>10%) over a 6 month period.[7] The disease represents 11% of all B cell malignancies, and is considered relatively curable, owing to recent advancements in anti-tumour combination chemotherapies and involved-field radiation therapy (IFRT).[6,8]

HL can be further subdivided into classical (cHL) or nodular lymphocyte predominant. The former is characterised by the presence of mono- (Hodgkin) or multinucleated (Reed-Sternberg) neoplastic cells termed Hodgkin Reed-Sternberg (HRS) cells.[9] With a bimodal age distribution of occurrence, the pathogenic mechanisms leading to development of cHL are thought to include both environmental and genetic factors, with a strong association with Epstein Barr virus (EBV) co-infection and human leukocyte antigen (HLA) genotypes I and III.[9,10] Tumour composition and progression is remarkably consistent between individual cases of cHL, a factor that has contributed to the success of current therapies.[11,12]

Whilst these therapies have shown great clinical efficacy, higher than acceptable drug-associated toxicities and patient relapses represent the current clinical challenges of the disease. In recent years, fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) has been used to tailor first and second line therapies for cHL patients. ^{18}F-FDG-PET has shown considerable potential in improving clinical outcomes, sparing low-risk patients from overly aggressive treatments and accurately identifying high-risk patients whom may benefit from changes to standard therapy.[13] Further research is, however, required to better define what constitutes a positive or negative scan, elucidate the factors which influence tracer uptake, and determine the optimal timing for when such scans should be performed.[13] Increased risk of secondary neoplasms, cardiovascular and pulmonary disease, are other clinical challenges faced in the management of long-term survivors of cHL.[7] Whilst advancements in radiotherapy, which have led to a reduction in the number of cycles and intensity of combination chemotherapies required, have been linked to a slight decline in risk of secondary malignancies, death from non-HL disease is still greater in this cohort relative to the general population.[7,14] Following from this, the advent of new therapies and ongoing clinical trials has further emphasised the need for long-term follow up in cHL patients, to assess drug efficacy and late developing side effects. Finally, poor prognosis and death due to non-HL disease is a current challenge faced by older cHL patients.[7] Relative to their younger counterparts, older cHL patients have been associated with an increased number of comorbidities and an inability to tolerate intensive treatment regimes, making delivery of first line therapies difficult.[7] Future treatment strategies must look towards addressing the issues surrounding current therapy intensity and side effects to improve outcomes for patients.

This review investigates how our current understanding of the pathogenesis of cHL is shaping the targets for future therapies, which aim to combat the clinical challenges raised by current disease management. Current therapy targets and efficacy will be considered in contrasts to novel therapies, their modality, side effects and expected efficacy.

Methods

Information for this paper was collected using the PubMed and UpToDate databases. Papers were selected based on relevance, using a combination of the search terms; Hodgkin lymphoma, classical Hodgkin lymphoma, pathogenesis, treatment and current therapies. Any therapies found by this search, were then searched for directly using the drug name. Data with respect to non-Hodgkin lymphoma was excluded. Articles referencing data specific to classical Hodgkin lymphoma was included. A total of 42 papers were collected for use, from June 2014 to June 2015, with papers

selected post 2009 for novel therapies and post 1995 for those regarding pathogenesis of cHL.

Pathogenesis of Classical Hodgkin Lymphoma

B cell lymphomas are characterised by their phenotypic resemblance to features of normal B cells during development. In the case of cHL, HRS cells are thought to be derived from a pool of pre-apoptotic germinal center B cells, which have lost the capacity to express B cell receptor.[6] For a given case of cHL, studies of the HRS cell population indicate identical immunoglobulin (Ig) gene rearrangement and somatic hypermutation, implicating the clonal expansion of a malignant cell population of mature, post germinal center origin.[9] Set upon a non-malignant, inflammatory background of lymphocyte infiltrate, HRS cells exhibit distinct features including a lack of B cell receptor and positivity for phenotypic markers such as TARC, CD15, Pax-5, MUM-1, CD138 and CD30.[15] The lymphocyte infiltrate and expression of these specific surface receptors promotes the survival of this neoplastic cell population through paracrine signalling and immune suppression of anti-tumour responses.

The disease is also characterised by its links with environmental and genetic factors. Associated with one-third of all diagnosed cases of cHL in the developed world, EBV gene expression is thought to promote B cell survival, transformation and reprogramming towards a HRS cell phenotype.[9] Following primary infection, EBV becomes latent in the host memory B cell population, such that it can persist for the lifetime of the cell. EBV encoded EBNA-1 and LMP-1 gene products are thought to be essential for the transformation of memory B cells.[9] These gene products act on intracellular signalling pathways, where EBNA-1 acts directly to down regulate tumour-suppressor gene expression, as well as supporting tumour development through up-regulation of CCL22, which promotes T regulatory cell activation.[5] Similarly, LMP-1 gene product mimics the signal conferred by CD40, which acts downstream to activate NF-κB, p38, PI3K, AP1, and JAK-STAT signalling to promote cell survival.[16,17] Genetic studies have also shown that crippling mutations in Ig genes, which encode the B cell receptor, are almost exclusively associated with EBV positive cases of cHL. This link is thought to be related to the EBV encoded gene LMP-2, which appears to reprogram mature B cells towards a HRS cell phenotype, promoting the rescue of germinal center B cells, lacking a B cell receptor, from apoptosis.[9]

The bimodal age distribution observed in cHL is supported by the delayed exposure theory.[18] This theory links socioeconomic status to delayed childhood exposure to common pathogens, such as EBV, which has been associated HL development in young adults.[18] Epidemiological studies have linked increased risk of HL development in young adults to high maternal education, small sibship size, low housing density, and other correlates of high socioeconomic status.[18-20] These factors are thought to delay exposure to common childhood infections, and result in increased severity of disease upon exposure in later life.[18] In the case of EBV exposure and cHL, high socioeconomic status has been linked to increased risk of developing EBV-positive cHL in adolescence (15-39 years), whereas late onset cHL (55-79 years) is typically EBV-negative and associated with lower socioeconomic status.[18]

A strong correlation exists between EBV-associated cHL and particular HLA genotypes.[10] Cytotoxic T lymphocytes (CTLs) play a crucial role in the management of EBV infections, where their response is dependent on antigen presentation by HLA's on antigen presenting cells. Association studies have identified areas within HLA class I and class III regions of the genome, in particular alleles 126 and 284 of micro-satellite markers D6S265 and D6S510 respectively, which are linked to increased susceptibility to cHL.[10] Specifically, these regions of variance have been linked to EBV positive cases of cHL, suggesting that HLA mediated antigen presentation plays a crucial role in the pathogenesis of the disease. It is thought that in susceptible individuals, the weakened CTL response enables enhanced expansion of EBV-infected cells, with elevated titres of the virus promoting B cell transformation.[9]

After transformation, survival of the HRS cell population is dependent on the dysregulation of the cell fate through an inflammatory response which modulates a family of transcription factors, nuclear factor (NF)-κB, that enable the evasion of apoptotic pathways. Under normal conditions, NF-κB is present in an inactive state in the cell cytoplasm, transiently activated under the tight control of stimulatory signals. In the HRS cell population, NF-κB becomes inappropriately activated to confer cell

survival and proliferation signals. This inappropriate activation is thought to be the consequence of EBV virus LMP-1 gene expression, which confers intrinsic signals for the up regulation of NF-κB in EBV positive tumours.[9] Alternatively, in EBV negative instances of cHL, over expression of cell surface receptors (CD30), acquisition of deleterious mutations (in A20) or loss of regulatory proteins (IκB), promote the sustained signalling of NF-κB.[9] NF-κB activation confers a 'rescue' signal to germinal center B cells that are destined for apoptosis, due to their inability to express a B cell receptor. As this cell population persists, the cells undergo uncontrolled clonal expansion, acquiring additional mutations, which drive them towards the malignant HRS cell phenotype. The HRS cells then secrete a milieu of cytokines, which promote the accumulation of the non-malignant inflammatory infiltrate characteristic of cHL. Together, this tumorous mass forms an environment conducive to the continued survival of the HRS clone.

Diagnosis and staging of classical Hodgkin Lymphoma

The diagnosis and staging of cHL is crucial to the management and treatment of the disease. Identified by the presence of HRS cells, the disease is most commonly diagnosed via light microscopy and immunohistochemistry of tissue biopsies exhibiting lymphadenopathy, preferably through obtaining an entire lymph node from the affected region.[21] Once a cHL diagnosis has been confirmed, staging tests are conducted to determine the extent of disease. Previously, bone marrow biopsy was a necessary component of staging, however recent utilisation of non-invasive whole body imaging procedures, such as computed tomography (CT) and positron emission tomography (PET) scans, allow the clinical staging of cHL with no detrimental impact on patient treatment or outcomes.[22] Along with imaging, laboratory studies are also conducted to assist in the determination of the optimal course of therapy. These tests include complete blood count, absolute lymphocyte count, erythrocyte sedimentation rate, HIV serology, pregnancy test in women of childbearing age and liver, bone, and renal function biochemical tests.

Currently, clinical staging of cHL adopts the Cotswold-modified Ann Arbor classification system, which considers the number of sites involved, type of tissue involvement (nodal versus extranodal) and the distribution of disease (See Table 1).[23] This staging method identifies patients as either early (Stage I and II) or advanced (Stage III and IV) stage disease. Early stage disease can be further stratified based of the presence or absence of certain prognostic features, which also influence the treatment strategy adopted.[7] This stratification is termed favourable or non-favourable disease prognosis and has been defined by the German Hodgkin Study Group (GHSG) and the European Organisation for the Research and Treatment of Cancer (EORTC) (See Table 2).[7]

Table 1: Cotswold-modified Ann Arbor Classification (23)

Stage	Tissue Involvement
I	Single lymph node region (I) or one extralymphatic site (IE)
II	Two or more lymph node regions, same side of the diaphragm (II) or contiguous extralymphatic extension plus one or more lymph node regions same side of the diaphragm (IIE)
III	Lymph node regions on both sides of the diaphragm (III), which may be accompanied by contiguous extralymphatic extension (EIII)
IV	Diffuse involvement of one or more extralymphatic organs or sites
Suffix	**Features**
A	No B symptoms
B	Presence of at least one of the following: unexplained weight loss >10% of baseline during a 6 month period prior to staging; recurrent unexplained fever >38°C; recurrent night sweats
X	Bulky tumor is defined as either a single mass of tumour tissue exceeding 10cm in largest diameter or a mediastinal mass exceeding one-third of the maximum transverse transthoracic diameter measured on a standard posterior-anterior chest radiograph.

Table 2: Comparison of the Prognostic Factors for the Determination of Early Stage Disease in classical HL (7)

Prognostic Factors	Favourable Early Stage Prognosis		Unfavourable Early Stage Prognosis	
	GHSG	EORTC	GHSG	EORTC
Large Mediastinal Adenopathy	✗	✗	✓	✓
ERS <50, without B symptoms	✓	✓	✗	✗
ERS <30, with B symptoms	✓	✓	✗	✗
Extranodal Disease or Age	✗	≤ 50 years	✓	> 50 years
Number of lymph node sites involved	1-2	1-3	≥3	≥4

For patients with advanced stage disease, risk stratification tools can be useful to identify patients at risk of standard treatment failure and who may benefit from a modified or intensified treatment regime.[24] The International Prognostic Index (IPI) is the most widely used scoring system, which predicts 5-year freedom from progression and overall survival rate.[24,25] However, whilst the IPI is widely used, its lack of consideration for advancements in treatment has meant it is yet to be proven useful for the determination for initial therapy in disease.

Current treatment of Classical Hodgkin Lymphoma

As stated previously, the clinical staging and prognostic features for a given case of cHL largely influences treatment selection and management strategy for patients. Standard first line therapy for early stage favourable cHL involves 2 cycles of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) chemotherapy in combination with 20 Gy IFRT.[7] Emerging evidence suggests that PET scans may be used to tailor treatment therapies and reduce treatment intensity through omission of IFRT.[13] However, research in this area is ongoing, with some finding that whilst initial outcomes are similar in early PET-negative patients opting for or against IFRT, the risk of early relapse is significantly higher in those who omitted irradiation.[26] Conversely, early stage unfavourable cHL requires 4 cycles of ABVD chemotherapy in combination with 30 Gy IFRT.[3] For patients with advanced stage cHL, 6-8 cycles of ABVD or 6 cycles of escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone) are recommended as the first line therapy.[7] Studies comparing the efficacy of combination chemotherapies, ABVD and BEACOPP, in advanced stage cHL, have identified that whilst escalated BEACOPP is associated with improved initial tumour control, it is also linked to increase rates of fatal acute toxicities and secondary leukaemia.[7,27] Furthermore, BEACOPP based therapy are associated with increased risk of direct side effects of chemotherapy, infectious complications, blood product requirements, infertility and the development of secondary acute myeloid leukaemia.[7] As the long-term outcomes for both treatment options are similar, therapy selection is often influenced by patient preference with regards to the balance between drug efficacy and toxicity.

After first line therapy, approximately 80% of cHL patients achieve long-term remission.[1] However, within this population, drug-associated toxicities result in an increased mortality rate relative to the general population. Secondary neoplasms and cardiovascular disease represent the two major causes of non-relapse associated mortality for long-term survivors of cHL.[7] These outcomes are often associated with increased combination therapies involving IFRT, which may result in long-term anergic immunological responses and T cell defects.[7] Pulmonary toxicity is another major side effect of bleomycin-containing chemotherapies, with outcomes ranging from reduction in diffusion capacity, lung volume and vital capacity to pneumonitis and end-stage pulmonary fibrosis.[7] Studies have demonstrated that 1-2% of bleomycin treated patients experience fatal pulmonary fibrosis.[7] Psychological problems have also been associated with this cohort, owing to therapy-induced infertility and reduction in quality of life.[7]

For the remaining 20%, disease relapse and progression is by far the major cause of death after first line therapy.[7] High-dose chemotherapy and autologous stem cell transplantation (SCT) represent the standard second-line treatment for refractory or relapsed cHL.[28] Of those to receive second-line treatment, approximately 50% of relapsed patients and a minority of refractory

patients will go on to achieve durable responses.[28] At present, allogeneic SCT represents the only strategy with curative potential for those remaining patients, however treatment has been associated with high mortality rate, due to resultant graft versus host disease or fatal infection post transplantation.[28] Whilst ^{18}F-FDG-PET has been beneficial in identifying patients in whom allogeneic SCT is expected to have the greatest effect, overall survival (40-85%) and progression free survival (23-40%) remains low.[13,28] In addition, the prognosis of patients who fail high dose chemotherapy and autologous SCT is poor.[28] Therefore, novel therapies are needed to minimise current combination therapy associated toxicities and improve patient outcomes in the primary resistant and relapsed populations of cHL.[28]

Future direction of therapies for classical Hodgkin Lymphoma

The future direction of cHL treatment looks towards agents that are highly specific for the neoplastic HRS cell population and their characteristic non-neoplastic inflammatory infiltrate microenvironment. Advancements in genomic sequencing have allowed for the identification of numerous aberrant signalling pathways specific to HRS cells and their microenvironment, which present potential targets for small-molecule therapies.[11] These therapies aim to diminish the prosurvival signals and anti-apoptotic pathways conferred by the inflammatory infiltrate present in cHL, as well as target HRS cells by radiation-emitting immune conjugates.[12] Since 1977, Brentuximab vedotin has been the only new therapy approved by the Food and Drug Administration for the treatment of cHL, illustrating the stark need for further research in this area.[11] Ongoing clinical trials, examining the efficacy of immunotherapies and small-molecule therapies targeting oncogenic signalling pathways, appear promising (See Figure 1).[29-33]

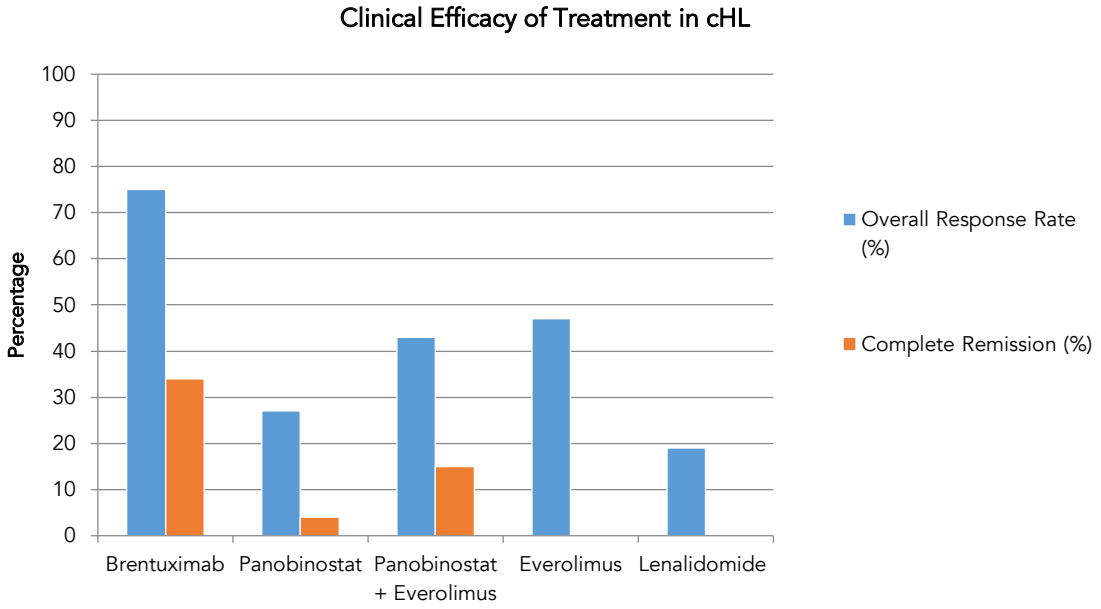

Figure 1. Phase I and Phase II clinical trials using current and novel therapies in the treatment of patients with relapsed or refractory cHL.

Immunotherapies

Brentuximab vedotin, the most successful immunotherapy to date, is an antibody-drug conjugate, targeted against the CD30+ HRS cells pathognomonic of cHL.[32] Associated with minimal severe adverse side effects, Brentuximab is currently used in the treatment of relapsed or refractory cHL patients, with phase I and II clinical trials demonstrating an overall response rate of 75% and complete remission in 34% of patients.[32,34] Since then, various other monoclonal antibody therapies have entered clinical trials for the treatment of cHL. Whilst CD20 is not constitutively present on HRS cells, anti-CD20 therapies such as rituximab are used to target the inflammatory constituents of the microenvironment. The rational for targeting CD20

is to eliminate cells such as tumour-supportive reactive B cells and putative HL-initiating cells, which are CD20 positive and confer pro-survival and progression signals to HRS cells.[12] Phase II clinical trials have demonstrated an overall survival rate of 96-98% for newly diagnosed patients treated with rituximab in combination with ABVD chemotherapy, relative to the 94% achieved by ABVD alone.[35,36] In addition, other monoclonal antibody therapies targeting the reactive inflammatory microenvironment observed in cHL have been developed. Alemtuzumab and Nivolumab are monoclonal antibodies against CD52 and PD1 respectively, which target the T cell contingent of the characteristic inflammatory infiltrate of cHL. These drugs act to either dampen the T cell response by antibody mediated lysis or alternatively enhance the anti-tumour response through improved T cell receptor signalling.[11,12] Comparative clinical trials for these drugs in cHL patients are limited, however, preliminary data for Nivolumab is promising, with its use in relapsed or refractory HL patients achieving a response rate of 87% and complete remission in 17% of patient.[37]

Antibody mediated immunotherapies have shown efficacy in clinical trials, however, they are limited by their short half-life and need for repeat infusions. For this reason, interest has shifted towards adoptive immunotherapies to generate host directed, memory responses against tumour cells. Whilst weakly immunogenic, EBV latent membrane proteins, LMP1 and LMP2, have proved attractive targets for immunotherapy via EVB-specific CTLs in recent clinical studies on patients with EBV positive HL. These trials have shown that EBV-specific CTLs are generally well tolerated in patients post infusion, demonstrating biological activity and the capacity to induce complete or partial remission in patients with heavily pre-treated cHL.[38] The benefit of EBV-specific CTL adoptive immunotherapies is the potential for the generation of a memory T cell pool, conferring long-lived immunity, with minimal toxicities that do not eliminate healthy tissues.[39] However, whilst high cure-rates are achievable, results are not consistent and treatment is limited by the ability to expand sufficient autologous CTLs from heavily pre-treated patients with relapsed disease.[39] In addition, the ability to generate a long-lived memory response has proven difficult owing to the weakly immunogenic nature of LMP1 and LMP2, and the tendency of tumour cells to modulate the expression of targeted antigen to enhance survival. Research is currently under way investigating combination EBV-specific CTLs targeting both LMP1 and LMP2, demonstrating improved results.[39]

Abbreviations:

- JAK/STAT – Janus Kinase / Signal Transducer and Activators of Transcription
- NF-κB – Nuclear Factor Kappa Beta
- PI3K – Phosphatidylinositol-3 Kinase
- MEK/ERK – Mitogen-activated Extracellular-signal regulated Kinase / Extracellular-signal Related Kinase
- Akt – Protein Kinase B
- mTOR – Mammalian Target of Rapamycin

Small Molecule Therapies

Alternatively, to immunotherapies, further advancements and understanding into the oncogenic signalling pathways, which sustain the neoplastic cell population of cHL, have allowed for the development of new small molecule therapies. Studies have shown, the JAK/STAT, NF-κB, PI3K and MEK/ERK pathways are all constitutively active in HRS cells, conferring pro-survival, metabolism and immunity signals.[11,33] Current clinical interest is focused on the PI3K/Akt/mTOR pathway, which contributes to the constitutive activation of NF-κB.[33] Everolimus and Temsirolimus are two analogues of rapamycin, which serve as mTOR inhibitors, and are currently undergoing clinical trials. Everolimus acts to down regulate the activation of NF-κB, inhibiting the subsequent survival signals, whilst Temsirolimus induces cell cycle arrest.[33] Clinical trials in patients with relapsed cHL treated with Everolimus observed an overall response rate of 42%, which was generally well tolerated patients, with most patients going off the trial due to disease progression rather than due to drug associated toxicities.[11,33] Conversely, JAK and NF-κB inhibitors have proven to be theoretically viable treatment options for relapsed cHL, however preliminary trials have shown minimal to no clinical significance as of yet.[11] The encouraging overall response rate and ability to induce stable disease make mTOR inhibitors the current leading therapy in oncogenic signalling pathway treatments for those with relapsed cHL.

Another avenue currently being explored for the treatment of resistant and relapsed cHL is epigenetic therapies. Histone deacetylase (HDAC) inhibitors, such as Panobinostat, have demonstrated direct and indirect antitumour clinical activity. This group of drugs is thought to exert its effects through induction of cell-cycle arrest and apoptosis,

inhibition of angiogenesis and promotion of an antitumour microenvironment and immune response.[40] *In vitro* studies have demonstrated HDAC inhibitors modulate the activity of transcription factors to either down regulate the expression of chemokines such a TARC, disrupt PD1 and PDL1 signalling, or up regulate the expression of OX40L, TNFα and IL-17 to promote an anti-tumour microenvironment.[40,41] Panobinostat is considered the most potent HDAC inhibitor against cHL, with the highest single agent activity due to its ability to target multiple cellular pathways.[40] Recent Phase II clinical trials in relapsed cHL patients observed a reduction in tumour size of 74%, with 4% of patients achieving complete remission and 23% achieving partial remission.[40] The drug is generally well tolerated, with studies reporting grade 1 to 2 side effects, including diarrhea, nausea, vomiting, fatigue and haematological effects such as thrombocytopenia, anaemia and neutropenia.[29]

The unselective nature of Panobinostat means it is capable of exerting its effects on a wide range of signalling pathways and effector molecules within malignant cells. For this reason, Panobinostat is also being considered as a potential therapy to improve the efficacy of other drugs in the treatment of cHL. Studies examining HDAC inhibitors in combination with other small molecule therapies have demonstrated a synergistic effect between the two types of drugs. Independently, Panobinostat and Everolimus demonstrate modest clinical activity as single agents in the treatment of refractory cHL. However, in a recent Phase I trial, the combination therapy of Panobinostat and Everolimus in relapsed classical HL generated an overall response rate of 43%, with 15% achieving complete remission.[30] The improved efficacy of these therapies in combination is attributed to the ability of these drugs to target multiple sites within a common signalling pathway. However, due to the multifactorial effect of the drugs in combination, additive toxicities are a concern in the progression of this therapy option.

Finally, immunomodulation is an alternative therapeutic option for the treatment of cHL. Lenalidomide is an immunomodulatory drug, currently being investigated for its efficacy in cHL patients who have progressed past first line therapy. Whist the mechanism of action are incompletely understood, it is thought Lenalidomide causes direct induction of apoptosis and anti-angiogenesis in the neoplastic cell population, as well as activation of immune effector cells.[42] Due to its multimodality, Lenalidomide is currently being investigated as a single-agent therapy for those who have failed conventional therapies.[42] Clinical trials of oral daily lenalidomide have yielded clinical responses and disease stabilisation in heavily pre-treated HL patients. The drug has also shown high patient tolerability, with the most common drug limiting toxicities including cytopenias, rash and hepatic toxicity.[11] Lenalidomide appears to be a strong candidate for future therapies in patients with tumour resistance to conventional combination chemotherapies and offers minimal adverse effects.

Conclusion

The future direction of treatment for classical HL lies in targeted small molecule and immunotherapies, used in conjunction with existing treatment regimes, for the management of refractory and relapsed patients. Whilst novel therapies, such as Panobinostat and Everolimus combinations and Lenalidomide, have shown a relative reduction in drug-associated toxicities, their efficacy is yet to match that of existing treatments. Future research should look towards not only optimising the efficacy of novel therapies, but also consider the refinement and enhancement of existing prognostic tools and standard treatments. This will enable the customisation of cHL therapy for patients based on prognostic features, minimising overly aggressive treatments in good prognosis patients and accurately identifying poor-risk patients whom may benefit from changes to standard therapy. Future challenges will be met in achieving equivalent drug efficacy in novel therapies relative to those existing, and the refinement of existing prognostic tools to enable the individualised management of patients with cHL.

What is known already:	What this study adds/ highlights:
• The pathogenesis and phenotypic markers of the classical Hodgkin lymphoma malignant cell population	• Identification of the gaps existing in the treatment of classical Hodgkin lymphoma • Synthesis of current findings from ongoing clinical trials investigating novel therapies for the treatment of classical

• Existing therapies; their targets, efficacy and side effects	• Evaluation of which therapies appear most efficacious • Suggestion as to the future direction of treatment for classical Hodgkin lymphoma. •

References

1. Eichenauer DA, Engert A. Antibodies and antibody-drug conjugates in the treatment of Hodgkin lymphoma. European journal of haematology. 2014;93(1):1-8.
2. Armitage JO. Early-stage Hodgkin's lymphoma. The New England journal of medicine. 2010;363(7):653-62.
3. Marri PR, Ansell SM. Progress in the initial management of Hodgkin's Lymphoma. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis. 2013;49(1):12-8.
4. Warrington R, Watson W, Kim HL, Antonetti FR. An introduction to immunology and immunopathology. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2011;7 Suppl 1:S1.
5. Matsuki E, Younes A. Lymphomagenesis in Hodgkin lymphoma. Seminars in cancer biology. 2015.
6. Kuppers R. Mechanisms of B-cell lymphoma pathogenesis. Nature reviews Cancer. 2005;5(4):251-62.
7. Follows GA, Ardeshna KM, Barrington SF, Culligan DJ, Hoskin PJ, Linch D, et al. Guidelines for the first line management of classical Hodgkin lymphoma. British journal of haematology. 2014;166(1):34-49.
8. Steidl C, Connors JM, Gascoyne RD. Molecular pathogenesis of Hodgkin's lymphoma: increasing evidence of the importance of the microenvironment. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(14):1812-26.
9. Farrell K, Jarrett RF. The molecular pathogenesis of Hodgkin lymphoma. Histopathology. 2011;58(1):15-25.
10. Diepstra A, Niens M, Vellenga E, van Imhoff GW, Nolte IM, Schaapveld M, et al. Association with HLA class I in Epstein-Barr-virus-positive and with HLA class III in Epstein-Barr-virus-negative Hodgkin's lymphoma. Lancet. 2005;365(9478):2216-24.
11. Batlevi CL, Younes A. Novel therapy for Hodgkin lymphoma. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2013;2013:394-9.
12. Aldinucci D, Gloghini A, Pinto A, De Filippi R, Carbone A. The classical Hodgkin's lymphoma microenvironment and its role in promoting tumour growth and immune escape. The Journal of pathology. 2010;221(3):248-63.
13. Kasamon YL, Wahl RL. FDG PET and risk-adapted therapy in Hodgkin's and non-Hodgkin's lymphoma. Current opinion in oncology. 2008;20(2):206-19.
14. eMieux MH, Solanki AA, Mahmood U, Chmura SJ, Koshy M. Risk of second malignancies in patients with early-stage classical Hodgkin's lymphoma treated in a modern era. Cancer medicine. 2015;4(4):513-8.
15. Nishikori M, Uchiyama T. Molecular pathogenesis of Hodgkin lymphoma. International journal of hematology. 2006;83(5):398-403.
16. Young LS, Murray PG. Epstein-Barr virus and oncogenesis: from latent genes to tumours. Oncogene. 2003;22(33):5108-21.
17. Baumforth KR, Birgersdotter A, Reynolds GM, Wei W, Kapatai G, Flavell JR, et al. Expression of the Epstein-Barr virus-encoded Epstein-Barr virus nuclear antigen 1 in Hodgkin's lymphoma cells mediates Up-regulation of CCL20 and the migration of regulatory T cells. The American journal of pathology. 2008;173(1):195-204.
18. Chang ET, Zheng T, Weir EG, Borowitz M, Mann RB, Spiegelman D, et al. Childhood social environment and Hodgkin's lymphoma: new findings from a population-based case-control study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2004;13(8):1361-70.
19. Grufferman S, Delzell E. Epidemiology of Hodgkin's disease. Epidemiologic reviews. 1984;6:76-106.
20. Alexander FE, Ricketts TJ, McKinney PA, Cartwright RA. Community lifestyle characteristics and incidence of Hodgkin's disease in young people. International journal of cancer Journal international du cancer. 1991;48(1):10-4.
21. Eichenauer DA, Engert A, Andre M, Federico M, Illidge T, Hutchings M, et al. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2014;25 Suppl 3:iii70-5.
22. El-Galaly TC, d'Amore F, Mylam KJ, de Nully Brown P, Bogsted M, Bukh A, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(36):4508-14.
23. Kwee TC, Kwee RM, Nievelstein RA. Imaging in staging of malignant lymphoma: a systematic review. Blood. 2008;111(2):504-16.
24. Moccia AA, Donaldson J, Chhanabhai M, Hoskins PJ, Klasa RJ, Savage KJ, et al. International Prognostic Score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(27):3383-8.
25. Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(14):2373-80.
26. Raemaekers JM, Andre MP, Federico M, Girinsky T, Oumedaly R, Brusamolino E, et al. 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 : official journal of the American Society of Clinical Oncology. 2014;32(12):1188-94.

27. Engert A, Diehl V, Franklin J, Lohri A, Dorken B, Ludwig WD, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(27):4548-54.
28. Castagna L, Carlo-Stella C, Mazza R, Santoro A. Current role of autologous and allogeneic stem cell transplantation for relapsed and refractory hodgkin lymphoma. Mediterranean journal of hematology and infectious diseases. 2015;7(1):e2015015.
29. Younes A, Sureda A, Ben-Yehuda D, Zinzani PL, Ong TC, Prince HM, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: results of a phase II study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(18):2197-203.
30. Oki Y, Buglio D, Fanale M, Fayad L, Copeland A, Romaguera J, et al. Phase I study of panobinostat plus everolimus in patients with relapsed or refractory lymphoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2013;19(24):6882-90.
31. Fehniger TA, Larson S, Trinkaus K, Siegel MJ, Cashen AF, Blum KA, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood. 2011;118(19):5119-25.
32. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(18):2183-9.
33. Johnston PB, Inwards DJ, Colgan JP, Laplant BR, Kabat BF, Habermann TM, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. American journal of hematology. 2010;85(5):320-4.
34. Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. The New England journal of medicine. 2010;363(19):1812-21.
35. Younes A, Oki Y, McLaughlin P, Copeland AR, Goy A, Pro B, et al. Phase 2 study of rituximab plus ABVD in patients with newly diagnosed classical Hodgkin lymphoma. Blood. 2012;119(18):4123-8.
36. Kasamon YL, Jacene HA, Gocke CD, Swinnen LJ, Gladstone DE, Perkins B, et al. Phase 2 study of rituximab-ABVD in classical Hodgkin lymphoma. Blood. 2012;119(18):4129-32.
37. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. The New England journal of medicine. 2015;372(4):311-9.
38. Bollard CM, Aguilar L, Straathof KC, Gahn B, Huls MH, Rousseau A, et al. Cytotoxic T lymphocyte therapy for Epstein-Barr virus+ Hodgkin's disease. The Journal of experimental medicine. 2004;200(12):1623-33.
39. 3Bollard CM, Gottschalk S, Torrano V, Diouf O, Ku S, Hazrat Y, et al. Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(8):798-808.
40. Oki Y, Copeland A, Younes A. Clinical development of panobinostat in classical Hodgkin's lymphoma. Expert review of hematology. 2011;4(3):245-52.
41. Oki Y, Buglio D, Zhang J, Ying Y, Zhou S, Sureda A, et al. Immune regulatory effects of panobinostat in patients with Hodgkin lymphoma through modulation of serum cytokine levels and T-cell PD1 expression. Blood cancer journal. 2014;4:e236.
42. Boll B, Borchmann P, Topp MS, Hanel M, Reiners KS, Engert A, et al. Lenalidomide in patients with refractory or multiple relapsed Hodgkin lymphoma. British journal of haematology. 2010;148(3):480-2.