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Evolving Therapies in Relapsed and Refractory Hodgkin Lymphoma

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1. Introduction

Approximately 20% of Hodgkin Lymphoma (HL) patients do not achieve a durable remission or fail to respond to front-line chemotherapy. Despite the attempt to improve clinical outcomes by using the risk adaptive therapy, a significant number of patients die as a results of relapsed/refractory (rel/ref) disease.[1] Advances in understanding the etiology and molecular biology of HL are leading the development of novel therapeutic strategies that could be applied to improve clinical outcome of rel/ref HL patients. The pathologic features of HL reflect a defect in immune responses resulting from various cytokines and chemokines secreted partially by Hodgkin Reed-Sternberg (HRS) cells. HRS cells are unique in the way that they lost typical B cell gene expression pattern but retain the expression of surface molecules involving in antigen presentation (tumor necrosis factor receptor (CD30, CD40), CD80, MHC class II, and CD86). Aberration of Notch signaling pathway may contribute to their reprogramming.[2,3] Multiple genetic lesions, deregulated signaling pathway and transcription factors play important role in pathogenesis of HL including constitutive activation of nuclear factor kappa B (NFκB) and the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway.[4-6] Moreover, the role of the microenvironment in HL has been increasingly recognized. The majority of the cell population in HL-affected tissue is composition of the inflammatory cellular infiltrate, not the HRS cells that represents only small population (<1%). Understanding the complex relationship between the HRS cells and the microenvironment and chemokines milieu involved in its formation is crucial for the development of new therapeutic strategies.

In addition, Epstein Barr Virus (EBV) infection may plays a role in the pathogenesis of HL since it can influence the expression of certain chemokines (i.e. CXCL9, CXCL10, CCL3, and CCL5) that are highly expressed in HRS cells and the EBV gene encoding the latent membrane protein 1 (LMP1) can mimic constitutively active TNF receptor (via a CD40/CD40L interaction) and promote IκB turnover leading to activation of NFκB and downstream signaling events.[7] Ongoing efforts are focused in developing adaptive or adoptive immune therapies targeting EVB related proteins in rel/ref HL patients.

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This chapter will provide an overview of the emerging therapeutic strategies for patients with relapsed and refractory HL (rel/ref HL) that had failed standard front line therapy, salvage chemotherapy and high-dose chemotherapy and autologous stem cell support (HDC-ASCS).

2. Systemic chemotherapy

Salvage systemic chemotherapy is often used in patients with rel/ref HL failing HDC-ASCS. Response rates are modest and response duration is usually short. Participation in clinical trials evaluating novel therapeutic approaches is strongly recommended. On the other hand, two chemotherapy agents had proven anti-tumor activity in highly refractory HL patients: gemcitabine and bendamustine.

Gemcitabine had been studied in the rel/ref HL either as single agent or combination therapy (i.e. with Vinorelbine).[8,9] Favorable toxicity profile and significant clinical anti-tumor activity were observed in heavily pre-treated HL patients, with overall response rates (ORR) up to 70% when used in combination regimens.[10,11] On the other hand, the duration of response is limited stressing the need to develop novel therapeutic strategies or to use this agent as a bridge rel/ref HL patient into more definitive treatments (i.e. allogeneic bone marrow transplant or other cellular-based therapies).

Bendamustine hydrochloride is a bifunctional mechlorethamine derivative with alkylating and antimetabolite properties. The exact antitumor mechanism is unknown though it appears to crosslink macromolecules resulting in DNA damage and subsequently apoptosis. It may also inhibit mitotic checkpoints and induce mitotic catastrophe. Bendamustine showed marked antiproliferative and proapoptotic effects on HL cell lines.[12] Moskowitz et al reported the activity of single agent bendamustine in rel/ref HL that previously failed HDC-ASCT, allogeneic stem cell transplantation (AlloSCT) or ineligible for transplant.[13] In this phase II clinical trial, bendamustine was administered at a dose of 120 mg/m^2 for two consecutive days, every 28 days, for up to maximum of 6 cycles. Of evaluable 16 patients, there were 6 complete responses (CRs) (38%) and 6 partial responses (PRs) (38%) for an ORR of 75%. Further studies of both single agent bendamustine and in combination with other chemotherapy are warranted in rel/ref HL patients.

3. Passive immunotherapy targeting the tumor microenvironment and/or HRS cells (Table 1)

3.1 CD80 (B7-1)

Immunohistochemical analysis has shown strong expression of CD80 on HRS cells, antigen presenting cells (APCs), T-cells and activated B-cells but not on resting B-cells and plasma cells and is absolutely absent on CD34+ cells, making CD80 an excellent target in HL. Preclinical data demonstrated that an anti-B7-1 immunotoxin had significant anti-tumor activity in HL-cell lines and minimal toxicity to CD34+ hematopoietic stem cell.[14,15] Galiximab is a primatized IgG1 monoclonal antibody, which binds to CD80 with high affinity and induces cell death via antibody-dependent cell-mediated cytotoxicity (ADCC). Smith et al studied the clinical activity of single agent Galiximab in patients with rel/ref HL not eligible for or had failed HDC-ASCT/AlloSCT.[16] Galiximab was administered at a dose of 500 mg/m^2 weekly for 4 weeks followed by 500 mg/m^2 every 4 weeks until disease

Author	Agent	Study Design (Phase)	Patient population	Clinical Activity	Median Duration of Response	Adverse Reaction
Smith et al[10]	Galiximab	II	Rel/ref HL (N=30)	ORR 6.9%; 1 CR, 1 PR	2 responders progressed after 7.5 and 3 mo.	Gr 3-4 hypo-phosphatemia, elevated SGOT/ SGPT, infection
Freedman et al[20]	Lucatumumab	Ia/II	Rel/ref HL (N=28) or NHL (N=31)	Ia N=10: ORR 10%; 1 PR II N=18: ORR 17%; 3 PR	NR	Gr 3-4 asymptomatic/ reversible elevated amylase/lipase, SGOT/SGPT
Younes et al[23]	Rituximab	N/A	Rel/ref HL (N=22)	ORR 22%; 1 CR, 4 PR	DOR 8.7 mo. (3.3+-14.9 mo.)	NR
Corazzelli et al[26]	Rituximab + Gemcitabine, Ifosfamide, Oxaliplatin (R+GIFOX)	N/A	Rel/ref HL (N=21)	ORR 86%; 16 CR, 2 PR	NR	Gr 4 TCP, infection
Oki et al[27]	Rituximab + Gemcitabine	II	Rel/ref HL (N=33)	ORR 48%; 5 CR, 11 PR	FFS 2.7 mo.	Gr 3-4 neutropenia, TCP
Ekstrand et al[29]	Rituximab	II	CD20+ newly diagnosed and rel/ref NLPHL (N=22)	ORR 100%; 10 CR, 12 PR	FFP 10.2 mo.	Infusion related reaction, Gr 1 hematologic toxicities, No Gr 3-4 toxicity
Rehwald et al[30]	Rituximab	II	NLPHL or CD20+ relapsed cHL (N=14)	ORR 86%; 8 CR, 4 PR	Not reach at 20+ mo.	Infusion related reaction, Gr 1-2 chill, fever, rhinitis, nausea, pruritus, leucopenia, dizziness
Eichenauer et al[31]	Rituximab	II	Newly diagnosed stage IA NLPHL (N=28)	ORR 100%; 24 CR, 4 PR	NR	No Gr 3-4 toxicity
Schulz et al[32]	Rituximab	II	Rel/ref NLPHL (N=15); cHL (N=4)	NLPHL: ORR 94%; 8 CR, 6 PR HL: 3 CR	TTP 33 mo. OS not reached	NR

HL = Hodgkin Lymphoma; Rel/ref = relapsed/refractory; ORR = overall response rate; CR = complete response; PR = partial response; Gr = grade; NLPHL = Nodular lymphocyte predominant Hodgkin lymphoma; TTP = time to progression; FFP = freedom from progression; OS = overall survival; NR = Not reported; TCP = thrombocytopenia

Table 1. Monoclonal antibodies targeting HRS cells or accessory cells in relapsed/refractory Hodgkin Lymphoma.

progression or unacceptable toxicity. The results were disappointing with ORR of only 6.9% and very short median time to progression (TTP) of 1.6 month. The authors concluded that single agent galiximab seems to have minimal activity in heavily pretreated rel/ref HL.

3.2 CD40

CD40 is a member of TNFR family (TNFRSF5) that is constantly expressed in HRS cells. In addition, CD40+ HRS cells are surrounded by CD40L-expressing T-cell lymphocytes. The CD40/CD40L interaction contributes to the pathobiology of HL possibly by NFκB activation and increased autocrine growth factor CCL5 resulting in inhibition of apoptosis, increased proliferation and microenvironment formation.[17-19]

Lucatumumab is a monoclonal antibody targeting the transmembrane receptor CD40. The safety and clinical activity of lucatumumab (HCD122) was evaluated in both NHL and HL patients who have progressed after at least two previous therapies [NCT00670592].[20] Patients received lucatumumab at a dose of 3 or 4 or 6 mg/kg intravenous weekly for 4 weeks followed by a 4-weeks rest period. The maximum tolerated dose (MTD) and dose limiting toxicity (DLT) were 4 mg/kg and 6 mg/kg, respectively. DLTs were consisted of clinically asymptomatic and reversible grade 3-4 elevation of amylase/lipase or transminase enzymes. For rel/ref HL patients, three of eighteen (17%) patients in phase II study component achieved a PR.

3.3 CD52

CD52 is highly expressed in surrounding reactive B-cells, T-cells and monocytes, although not on HRS cells itself. Depleting CD52+ accessory cells, which appear to provide survival signals to HRS cells, may have therapeutic value. Alemtuzumab is a humanized monoclonal antibody directed against CD52 resulting in cell lysis via antibody dependent cellular-mediated cytotoxicity. A phase II study addressing the clinical efficacy of alemtuzumab in rel/ref HL was unfortunately terminated due to slow accrual [NCT00129753].[21] Another phase II study focusing on the clinical outcome in rel/ref DLBCL and HL treated with alemtuzumab in combination with dose-adjusted EPOCH-Rituximab is currently enrolling patients [NCT01030900].[22]

3.4 CD20

A pilot study evaluating rituximab monotherapy in rel/ref HL has shown that depletion of B lymphocytes may has therapeutic potential.[23] The rationale of using rituximab in classical HL (cHL) is based on several laboratory and clinical observations: HRS stem cells express CD20 even though HRS cells infrequently express CD20, elimination of CD20+ B lymphocytes supporting HRS cells may deprive survival signals and improve immune response against HRS cell.[24,25] Studies of evaluating the addition of rituximab to conventional chemotherapy in patients with rel/ref cHL demonstrated promising results.[26,27] Copeland et al showed significant improvement of 5-year event free survival (EFS) in patients with newly diagnosed advanced stage cHL treated rituximab plus ABVD compared to historical data of patients treated with ABVD from the same institute.[28]

Targeting CD20 in patients with lymphocyte predominant HL (LPHL, had show to be an effective therapeutic strategy in contrast to other subtypes of HL. The efficacy of rituximab in LPHL was documented in several phase II studies with an ORR up to 100% in both relapsed and newly diagnosed patients.[29-32] Zojer et al and Schnell et al reported 2 cases of rel/ref HL patients treated with radiolabeled anti-CD20 monoclonal antibody, Yttrium-90 ibritumomab tiuxetan.[33,34] One patient had LPHL and another patient had cHL (lymphocyte rich) both achieved a complete remission following radioimmunotherapy (RIT). A Phase I/II study of safety and efficacy of I^{131} tositumomab rel/ref CD20+ cHL is currently enrolling patients [NCT00484874].[35]

4. Signaling pathway targets on HRS cells

4.1 CD30 signaling (Table 2)

CD30, a member of tumor necrosis factor receptor family (TNFR super family 8) involved in the activation of the canonical NFκB pathway and provides tumor cell survival signaling. CD30 is express in almost 100% of the HRS cells and serve as an attractive target of immunotherapy for cHL.[36,37] Borchmann et al had summarized the upsides and downsides of immunotherapy in HL.[38] Immunotoxins (ITs) containing ricin A, a ribosome inactivating protein, linked with surface marker CD30 as well as other ITs had shown disappointing clinical results with regard to response and toxicity in HL. Bi-specific constructs of monoclonal antibodies or molecules (BSMs) targeting CD30 and CD16 (NK cells) or CD64 (monocytes) were though well tolerated and showed some objective responses, production of BSMs is very expensive and time consuming. Low dose radioimmunotherapy (RIT), I-131 labeled anti-CD30 antibofy (131I-Ki-4) used in phase I trial in patients with relapsed HL showed some clinical activity with limitation to hematotoxicity particularly thrombocytopenia.[39] Better choice of radionuclides and the carriers would be necessary to

Author	Agent	Study Design (Phase)	Patient population	Clinical Activity	Median Duration of Response	Adverse Reaction
Ansell et al[41]	Iratumumab MDX-060	Phase I/II	Rel/ref HL (N=63)	4 responses; 2 CR, 2 PR	DOR 4 mo.	Gr 3 elevation of transaminase enzyme, epitaxis, anemia; gr3-4 dyspnea, cardiac temponade, ARDS
Younes et al[43]	Brentuximab vedotin	I	Rel CD30+ lymphomas (N=45; HL=43)	ORR 40%; CR 27%, PR 13% (for HL)	DOR 9.7+ mo. PFS 5.9 mo.	Peripheral neuropathy
Chen et al[44]	Brentuximab vedotin	II	Rel/ref HL (N=102)	ORR 75%; CR 34%	DOR not reach (for CR pts)	Peripheral neuropathy, neutropenia, TCP, anemia

HL = Hodgkin Lymphoma; Rel/ref = relapsed/refractory; ORR = overall response rate; CR = complete response; PR = partial response; Gr = grade; NLPHL = Nodular lymphocyte predominant Hodgkin lymphoma; DOR = duration of response; PFS = progression free survival

Table 2. Selected Clinical studies targeting CD30 in relapsed/refractory Hodgkin Lymphoma.

further development of this approach. Preclinical study targeting CD30 demonstrated significant anti-tumor activity.[40] Initial clinical studies evaluated naked antibodies targeting CD30 (MDX-030 and SGN-30) in patients with rel/ref HL. Both antibodies failed to demonstrate anti-tumor activity and in some cases accelerated tumor growth was observed upon CD30 binding by MDX-060.[41]

Previously unknown factors influenced the negative results observed in such trials such as 1) the agonist effects of the antibodies initially tested, 2) the modulation of CD30 in HRS cells (i.e. antigen shedding and/or internalization), and/or 3) impaired immune effector function in heavily pre-treated patients with HL. Two therapeutic approaches (i.e. development of drug conjugates or antibody re-engineering) had been explored clinically with significant improvement in clinical activity.

SGN-35 (brentuximab vedotin) is a drug conjugated designed to improve the clinical activity of SGN-30 in lymphomas. Brentuximab vedotin (SGN-35) is a antibody-drug conjugate containing the anti-tubulin agent, monomethylauristatin E (MMAE) linked to antiCD30 monoclonal antibody to enhance antitumor activity.[42]

Younes et al reported encouraging results in a phase I study of brentuximab vedotin in patients with relapsed CD30+ lymphomas.[43] Most of patients in the study had rel/ref HL (42/45), were heavily pre-treated (median number of previous regimens was 3), and almost 75% had previous HDC-ASCT. Seventeen patients had objective response including 11 CRs. Fifty percent (6/12) of patients who received maximum tolerating dose (MTD) (1.8mg/kg/dose) had objective responses.

Subsequently, a pivotal phase II of brentuximab vedotin in patients with rel/ref HL reported similar results.[44] All patients had failed HDC-ASCT and had median of 3.5 prior treatments. The ORR was 75% (76/102) with 34% of the patients achieving a CR (35/102). Currently, a randomized, double blind, placebo-controlled phase III study is evaluating SGN-35 versus placebo in patients at high-risk for residual disease after HDC-ASCT is ongoing [NCT01100502].[45] Brentuximab vedotin in combination with standard chemotherapy (ABVD) was now being evaluated in patients with newly diagnosed Hodgkin lymphoma stage IIA-IV [NCT01060904].[46] SGN-35 received fast track designation from the U.S. Food and Drug Administration (FDA) for the treatment of HL in 2009.

5. Downstream signaling targets (Table 3)

5.1 NFκB activity

As previously noted, constitutive activation of NFκB is one of the most important events in pathogenesis of HL and the result of multiple mechanisms. Downstream signaling of TNF receptors, expression of the EBV LMP1, and/or mutation of IκB gene have been described as the cause of constitutive NFκB activation. Inhibition of NFκB has been an area of drug development for the treatment of multiple hematological malignancies including HL. Pre-clinical data demonstrated that the proteasome inhibitor, PS-341 (Bortezomib) affects tumor cell proliferation and survival via inhibiting NFkB pathway, which is constitutively activated in HRS cells. As a result, bortezomib was evaluated in patients with rel/ref HL. The Cancer and Leukemia Group B (CALGB) conducted a phase II clinical trials (CALGB 50206) evaluating bortezomib monotherapy in rel/ref HL. Disappointingly, no clinical

activity was observed in treated patients.[47] The lack of anti-tumor activity of bortezomib in rel/ref HL was confirmed by two subsequent studies reported by Younes et al and Trelle et al.[48,49] More recent studies that evaluated bortezomib in combination with conventional chemotherapy showed mix results.[50,51]

Author	Agent	Study Design (Phase)	Patient population	Clinical Activity	Median Duration of Response	Adverse Reaction
Blum et al[47]	Bortezomib	II	Rel/ref HL (N=30)	9 SD	PFS 1.4 mo. OS 14.8 mo.	Gr 3-4 TCP
Youne et al[48]	Bortezomib	N/A	Rel/ref HL (N=14)	1 PR	NR	Gr 3 TCP, dyspnea and neutropenic fever
Trelle et al[49]	Bortezomib + Dexamethasone	II	Rel HL (N=12)	No response	NR	TCP
Mendler et al[50]	Bortezomib + Gemcitabine	N/A	Rel HL (N=18)	ORR 22%	NR	Gr 3 elevation of transaminase enzyme
Fanale et al[51]	Bortezomib + ICE	I	Rel/ref HL (N=13)	CR 33%; 9 Response (8/9 underwent HDC-ASCS)	NR	Gr 4 TCP 35%, Gr 4 neutropenia 18%
Kirschbaum et al[54]	Vorinostat	II	Rel/ref HL (N=25)	ORR 4%; 1 PR	PFS 4.8 mo.	Gr 4 anemia, lymphopenia, and Gr 3 TCP
Younes et al[57]	Mocetinostat	II	Rel/ref HL, (N=51)	110 mg: ORR 35%; 2 CR, 6 PR 85 mg: ORR 21%; 6 PR	NR	Gr 3 TCP, fatigue, neutropenia, non-fatal pericardial effusion
Dickinson et al[56]	Panobinostat	IA/II	Hematologic malignancies (N=128; HL=23 with 13 evaluable pts)	PR by CT 38%; PR by PET 58%	NR	TCP, neutropenia, febrile neutropenia, fatigue, anemia
Sureda et al[63]	Panobinostat	II	Rel/ref HL after ASCT (N=129)	ORR 27%; 5 CR, 30 PR	PFS 6.1 mo.	Gr 1-2 anemia, N/V/D, gr 3-4 TCP, aneima, neutropenia
Younes et al[68]	Entinostat	II	Rel/ref HL (N=23)	Disease control rate (CR+PR+SD) 65%	NR	Gr 1-2 GI causalities, fatique, pyrexia,; gr 3-4 TCP, anemia, neutropenia

Author	Agent	Study Design (Phase)	Patient population	Clinical Activity	Median Duration of Response	Adverse Reaction
Viviani et al[70]	Givinostat	II	Rel/ref HL (N=15; 13 evaluable pts)	7 SD (54%)	N	Gr 1 leukopenia, 1 diarrhea/ abdominal pain; Gr 2 TCP; 20% had QTc prolongation
Carlo-Stella et al[71]	Givinostat + Meclorethamine	II	Rel/ref HL (N= 35)	ORR 38%; CR 15%. PR 23%	OS 28 mo. TTP 3 mo.	Gr 1-2 nausea and fatigue; gr 3-4 TCP, anemia neutropenia
Johnston et al[75]	Everolimus	II	Rel/ref HL (N=19)	ORR 47%; 1 CR, 8 PR	TTP 7.2 mo.	Gr ≥3 pulmonary toxicity (4 pts)

HL = Hodgkin Lymphoma; Rel/ref = relapsed/refractory; ORR = overall response rate; CR = complete response; PR = partial response; Gr = grade; TCP = thrombocytopenia; TTP= time to progression; PFS = progression free survival; OS = overall survival; HDC-ASCS = high dose chemotherapy and autologous stem cell support; NR = Not reported

Table 3. Selected clinical studies evaluating target specific agents in relapsed/refractory Hodgkin lymphoma.

More potent and/or irreversible proteasome inhibitors (i.e. carfilzomib, MLN2238) had demonstrated high efficacy in rel/ref multiple myeloma and now are being evaluated in other hematologic malignancies.[52] However, their clinical activity in HL remains unknown.

5.2 Deacetylation of histone and other cellular proteins in HL biology: The therapeutic role of deacetylase inhibitors (DACi)

Gene expression profiling studies had demonstrated that HL is characterized by the silencing of key regulatory genes involved in B-cell maturation (i.e. CD79a, CD19, CD20, etc). In general gene expression is a tightly regulated process that is influenced by the 1) DNA/mRNA sequence, 2) expression/activity of transcription factors, 3) epigenetics (including the DNA, chromatin, and histone modifications); and 4) messenger RNA stability.

Post-transcriptional histone modification plays an important role in regulating gene transcription and is mediated by two groups of enzymes: histone acetyltransferase (HATs) and histone deacetylase (HDACs). The balance between HATs and HDACs is crucial in regulating the expression/function of several proteins involved in cell proliferation, cell cycle, apoptosis, angiogenesis, and immune regulation. Altering balance between HATs and HDACs had been found to be associated with various malignancies including HL.

To date, 18 HDACs have been identified in humans. HDACs are grouped in two major categories and four classes; zinc-dependent HDACs (Class I, II and IV) and NAD-dependent HDACs (Class III). Class I includes HDAC 1, 2, 3, 8, and 11; Class II includes HDAC 4, 5, 6, 7, 9, and 10; Class III includes homologues of yeast SIRT 1–7, and Class IV, which includes

only HDAC 11. As a group, HDAC are known to regulate several key cellular functions such cell proliferation, cell cycle, apoptosis, angiogenesis, migration, antigen presentation, and/or immune regulation. The activity spectrum of each HDAC is yet to be defined and there is overlap between the function of different HDAC regardless of their group or class.

HATs and HDACs interact also with non-histone proteins such as transcription factors (i.e. p53, STAT3, MYC , E2F, NFκB, etc.), α-tubulin, and chaperons (heat shock protein-90 [HSP90]), adding complexity to their cellular functions in normal and malignant cells. Given their influence in multiple regulatory pathways, HDACs became an attractive strategy to develop novel pharmacologic inhibitors for the treatment of cancer. Several pan- or selective-HDAC inhibitors (class I and IV) had been developed. Pre-clinical studies demonstrated significant anti-tumor activity in various cancer models including non-Hodgkin lymphoma and HL. Laboratory experiments suggest that HDAC inhibitors can induce cell cycle arrest, apoptosis or autophagy in cancer cell lines and can potentiate the anti-tumor activity of chemotherapy agents including proteasome inhibitors. Two HDAC inhibitors had been approved for the management of relapsed/refractory cutaneous T-cell lymphoma (vorisnostat and romidepsin). A second generation of more potent and selective (i.e. less toxic) of HDAC inhibitors (entinostat, panobinostat and MGCD103) had entered into clinical studies for patients with relapsed/refractory HL.

Vorinostat (SAHA), the first FDA approved HDAC inhibitor, is a potent inhibitor of class I and II HDAC and was the first of its class agent evaluated in patients with rel/ref HL. At the pre-clinical level, vorinostat has anti-proliferative and pro-apoptotic effects on HL cell lines by inducing p21 expression and down regulation of Bcl-xL respectively.[53] Kirschbaum et al presented on behalf of the South Western Oncology Group (SWOG), the results of a phase II clinical trial evaluating the safety and efficacy of Vorinostat in refractory/relapsed HL.[54] A total of 25 patients were treated with vorinostat at 200 mg given orally twice per day for 14 days every 21-day cycle. The activity of vorinostat was modest and only one patient achieved a partial remission (PR). Adverse events reported were similarly to those reported in vorinostat clinical trials in patients with cutaneous T-cell lymphoma (CTCL).

Preclinical data by Hartlapp et al demonstrated the activity of depsipeptide (**romidepsin**) in cHL cell lines *in vitro*.[55] In addition, the investigators demonstrated that romidepsin several cellular events leading to cell cycle arrest and apoptosis in HL cell lines such as and increased DNA binding capacity of RelA/p65, PARP-cleavage, decreased transcription of anti-apoptotic proteins (eg. XIAP, Bcl-xL), and down-regulation of STAT6. Romidepsin has not been formally evaluated in rel/ref HL patients.

An isotype-selective histone deacetylase inhibitor, **mocetinostat (MGCD-0103)**, inhibits class I and class IV and minimal class II HDAC inhibition. A phase II trial of 2 different doses (85 mg and 110 mg thrice weekly every 28 days) of mocetinostat in rel/ref HL had shown promising results with ORR of 38%.[56] The updated results from the same group demonstrated activity of single agent mocetinostat in heavily pretreated rel/ref HL with clinical responses observed in approximately 35% of patients with slightly better responses with 110 mg cohort.[57] Of 51 patients, 2 patients (110 mg cohort) achieved complete responses and 6 patients each from both cohort achieved partial response. Over eighty percent of patients in the study had previously failed HDC-ASCS and more than half of patients received four or more previous treatments. Serum thymus and activation-regulated

chemokine (TARC) or CCL17 which is highly expressed in HRS cells, decreased in patients treated with mocetinostat.[58] This findings were similar what had been previously observed following in vitro exposure of HL cell lines to vorinostat.[53] Together these findings, suggests that a decline in serum TARC may be a biomarker to predict clinical response to DAC inhibition therapy. Buglio et al found that MGCD0103 induced apoptosis in HL cell lines via the induction of TNFα expression and that inhibition of NF-κB activation with bortezomib resulted in synergistic anti-tumor activity.[59]

Bhalla et al observed similar findings with **PCI-24781**, a phenyl hydroxamic acid-based broad spectrum HDAC inhibitor.[60] PCI-24781 combined with bortezomib enhances apoptosis via reactive oxygen species (ROS), caspase activation (increased cleavage of caspase 8 and caspase 9), PARP activation, cell cycle arrest (G0/G1), and upregulation of p21 in HL cell lines and several non-Hodgkin lymphoma (Burkitt's lymphoma, follicular lymphoma, and large B-cell lymphoma) cell lines. While the biological interaction between bortezomib and multiple DAC inhibitors had been demonstrated in pre-clinical models and is been pursued in several clinical studies in multiple myeloma and mantle cell lymphoma patients, the limited activity of bortezomib as a single agent had damped the interest for pursuing this combination strategy in rel/ref HL patients.

Panobinostat (LBH-589) is a potent pan-HDAC inhibitor with anti-tumor activity observed in pre-clinical studies at nanomolar concentrations. Moreover, pre-clinical studies suggest that panobinostat is more potent than vorinostat in lymphoma pre-clinical models. Panobinostat was evaluated in phase IA/II study in 128 patients with advanced hematologic malignancies including rel/ref HL.[56] Patients received 2 schedules of oral administration (MWF every week at a dose of 20, 30, 40, 60, 80 mg/dose or MWF every other week at a dose of 30, 45, 60, 80 mg/dose). Out of 23 patients with rel/ref HL, 13 patients were evaluable for response. Five out of thirteen (38%) patients had PR by CT and 7/12 patients (58%) had metabolic PR by PET. The maximum tolerated dose (MTD) was 40 mg/dose every week schedule and the principal dose-limiting toxicity (DTL) was thrombocytopenia.

Younes et al confirmed efficacy of panobinostat in phase II study in patients with rel/ref HL.[61] Panobinostat was administered at a dose of 40 mg thrice weekly in 21-day cycle until disease progression. The update results showed encouraging clinical activity of panobinostat with 1 patient achieved CR and 10 pateints achieved PR.[62] Moreover, disease control rate (CR+PR+SD) was 79%. Panobinostat was well tolerated and reversible thrombocytopenia was managed by dose delay or dose reduction. The interim results for this phase II study continues to demonstrate encouraging activity of panobinostat.[63] The final results are currently not available. As previously demonstrated with other DAC inhibitors, a decrease in serum TARC levels was observed in panobinostat treated patients achieving an objective response (i.e. PR or CR).[64]

The safety and efficacy of the oral agent **belinostat (PXD-101)** was evaluated in patients with rel/ref NHL or cHL by Zain et al.[65] Tumor size reduction found in 1/3 of patients with HL using the recommended dose-schedule for patients with solid tumors (750 mg daily, D1-14 every 21days).

Entinostat (SNDX-275) is a class I isotype-selective HDAC inhibitor with longer half-life. Pre-clinical data from Khaskhely et al demonstrated *in vitro* activity in HL-derived cell lines.[66] Entinostat induced cell death with an IC50 of 0.4 μM. At the molecular level,

entinostat up-regulates p21 expression, increased H3 acetylation and down-regulates the anti-apoptotic X-linked inhibitor of apoptosis (XIAP) resulting in apoptosis. Moreover, the combination entinostat with gemcitabine or bortezomib has shown synergistic effects. Jóna et al found that entinostat down-regulates anti-apototic Bcl-2 and Bcl-xL expression without altering Mcl-1 or Bax levels and its effect was enhanced by two Bcl-2 inhibitors (ABT-737 and obatoclax).[67]

Younes et al recently presented an update of a phase II clinical study evaluating the safety and efficacy of entinostat as a single agent in relapsed/refractory HL.[68] Interim results from a phase II open-label multicenter study of entinostat (ENGAGE-501) administered in an alternate dosing schedule (the first stage: 10 mg every 14 days, 28-day cycle; the second stage: 15mg every 14 days beginning C1d15) showed that of 23 patients with rel/ref HL, 65% have disease control (CR+PR+SD). Entinostat was well tolerable with minimal AEs consisting of grade 1/2 fatigue, fever and GI symptoms. Serious grade 3/4 AEs were primarily hematological and consisted of thrombocytopenia (59.4%) and neutropenia (28.1%). Accrual into the study continues and the final results of this clinical trial are eagerly anticipated. Given the safety profile of and the long half-life of this promising agent, combination studies with chemotherapeutic agents based in pre-clinical studies are warranted to further define the role of entinostat in the management of HL.

Givinostat (ITF-2357) is a hydroxamate pan-HDAC inhibitor with anti-inflammatory properties. Furlan et al reported a phase I safety and pharmacokinetics study in healthy males.[69] They found no serious side effects and no organ toxicity. Several phase II studies of givinostat are in process to evaluate the safety and efficacy in rel/ref HL. A phase II open label non-randomized study by Viviani et al enrolled 15 patients with rel/ref disease, 13 patients had failed HDC-ASCT, and 4 of those patients had also failed an alloSCT.[70] Givinostat was administered at a dose of 100 mg orally daily in three 4-week cycles. Seven of 13 patients (54%) whom completed at least one cycle of therapy were evaluable for response, SD was observed in 46% of the patients. Toxicity includes grade 1-2 thrombocytopenia, leukopenia, diarrhea and/or abdominal pain; nonetheless, twenty percent of patients had transient drug discontinuation due to prolonged QTc. Another phase II study evaluated the safety and clinical activity of givinostat in combination with meclorethamine in patients with rel/ref HL.[71] Anti-tumor activity was observed and correlated with a reduction in serum TARC levels.

5.3 Targeting the PI3K/AKT/mTOR pathway in HL

Everolimus (RAD001) binds to FK506-binding protein 12 (FKBP12) forming a complex that has mTOR kinase inhibition activity, inhibit tumor cell proliferation and angiogenesis by decreasing hypoxia-inducible factor 1a (HIF1a) expression.[72,73] Everolimus demonstrated anti-proliferative effect in several solid tumor and hematologic malignancies including HL. Jundt et al showed that everolimus markedly suppress tumor cell proliferation of HL *in vivo* and down-regulates constitutively activated NFκB activity in HL cell lines.[74] A phase II trial evaluated the clinical activity and toxicity of everolimus in patients with heavily pretreated rel/ref HL (median of 6 prior therapies and 84% had prior HDC-ASCS).[75] Of 19 patients, one patient achieved CR, 8 patients achieved PR resulting in ORR of 47%, although median time to response was only 7.2 months.

Preclinical data from Georgakis et al showed **temsirolimus** (CCI-779) induced cell cycle arrest at G0/G1 phase and autophagy in HL-derived cell lines suggesting that this particular mTOR inhibitor may have therapeutic value in patients with HL.[76] Several phase I/II trials studying the safety and efficacy of single agent various mTOR inhibitors (i.e. temsirolimus or everolimus) monotherapy, or combination with lenalidomide or sorafinib are being conducted to test the concept of mTOR inhibition in treatment rel/ref HL.

5.4 Heat Shock Protein (HSP)

Heat shock protein acting as chaperones are essential in promoting cell survival by maintaining the structure and function of key regulatory proteins involved in cell cycle, proliferation and apoptosis. HSP over-expression had been demonstrated in several malignancies including HL. Inhibition of HSP is another attractive target in cancer therapeutics. Boll et al demonstrated the biological effects of a HSP90 inhibitor, **BIIB021** on HL-derived cell lines.[77] The investigators demonstrated that, BIIB021 inhibited the constitutive activity of NFκB independent of IκB mutation status and increased susceptibility of HL cells for NK cell-mediated killing via inducing the expression of activating NK-cell ligands. Schoof et al showed that inhibition of HSP90 by either geldanamycin derivative 17-AAG or RNA interference in HL cells led to decrease cell proliferation and inhibition of STAT1, STAT3, STAT5, and STAT6 tyrosine phosphorylation possible secondary to reduced protein expression of Janus kinase (Jaks).[78] HSP90 may be a promising target in patients with rel/ref cHL.

6. Immune therapy for rel/ref HL

6.1 Lenalidomide

Lenalidomide, a novel IMiDs® immunomodulatory drug is emerging as an attractive therapeutic option for patients with B-cell lymphoproliferative neoplasms, including HL. Studies in lymphoma and multiple myeloma (MM) models have demonstrated that lenalidomide exerts higher anti-tumor activity than thalidomide, has a unique capacity to enhance the innate immune system, enhance the anti-tumor activity of rituximab, and inhibit angiogenesis.[79,80] Abnormal immune response, increased angiogenesis, and apoptosis resistance, which contribute to the development of HL, support the scientific standpoint of evaluating lenalidomide in rel/ref HL.[81-83]

Lenalidomide was evaluated in patients with relapsed/refractory HL in three phase II clinical trials (Table 4). A phase II study presented by Böll et al and subsequently validated by Kuruvilla et al suggested lenalidomide had anti-tumor activity in rel/ref HL patients achieved a clinical response (CR or PR).[84,85] More importantly, lenalidomide monotherapy was well tolerated and toxicities were manageable. Fehniger et al reported similar anti-neoplastic activity in rel/ref HL patients.[86] Recently and as had been observed in other lenalidomide treated patients, tumor flare reaction (TFR) syndrome with sudden onset painful re-enlargement of tumor following early tumor shrinkage was reported in 3 cases of relapsed HL after hematopoietic stem cell transplantation which mimic tumor progression but manageable with anti-inflammatory/analgesic upon continuation of lenalidomide.[87]

Author	Agent	Study Design (Phase)	Patient population	Clinical Activity	Median Duration of Response	Adverse Reaction
Böll et al[84]	Lenalidomide	N/A	Rel/ref HL (N=42; 24 evaluable pts)	ORR 50%; 1CR, 11 PR	NR	Diarrhea, constipation, neuropathy, and mild dyspnea
Kuruvilla et al[85]	Lenalidomide	II	Rel/ref HL (N=15; 14 evaluable pts)	ORR 14%; 2 PR	TTP 3.2 mo. OS 9.1 mo	Gr 3-4 neutropenia, TCP, anemia; Gr 2 rash
Fehniger et al[86]	Lenalidomide	II	Rel/ref HL (N=38; 36 evaluable pts)	ORR 19%; 1 CR, 6 PR	NR	Gr 3-4 neutropenia, anemia, TCP, (4 discontinued d/t rash, elevated billirubin)

HL = Hodgkin Lymphoma; Rel/ref = relapsed/refractory; ORR = overall response rate; CR = complete response; PR = partial response; Gr = grade; TCP = thrombocytopenia; TTP= time to progression; NR = Not reported

Table 4. Clinical trials evaluating lenalidomide monotherapy in relapsed/refractory Hodgkin lymphoma patients.

6.2 EBV specific CTL therapy

In general, while chemotherapy agents, small molecule inhibitors, drug immunoconjugates or immunodulatory drugs exhibit promising anti-tumor activity in patients with rel/ref HL, the duration of response to each agent when reported by investigators is rather short. Giving the median age of patients with rel/ref HL the incorporation of therapeutic strategies with durable remissions is necessary. Two therapeutic approaches are been actively evaluated with promising results: 1) Autologous or allogeneic LMP2-specific cytotoxic T-cell lymphocytes (CTL) and 2) allogeneic bone marrow transplantation.

Approximately 30-40% of HL cases are associated with EBV infection of the HRS cells as proven by the expression of viral latent membrane protein (LMP).[88,89] EBV is known to induce the surface expression of three latent antigens in EBV-infected HRS cells: LMP1, LMP2 and Epstein Barr nuclear antigen 1 (EBNA1). Immunotherapy targeting EBV related proteins in HRS cells is an area of active translational research. The generation and ex vivo expansion of cytotoxic T-cell lymphocytes (CTLs) specific for one or more EBV antigens had been studied in patients with hematological malignancies such as post-transplant lymphorpoliferative disorders and rel/ref HL. In general two EBV-related immunotherapy approached had been studied: 1) adoptive immunotherapy (administration of autologous or allogeneic EBV specific CTLs) and 2) vaccination of relevant epitopes from one of the EBV antigens to boost the patients' own immune response.[90,91]

Lucas et al demonstrated the clinical efficacy of allogeneic EBV-specific CTLs in EBV-positive rel/ref HL who had previously failed HDC-ASCT.[92] Significant clinical activity was observed following allogenic CTLs infusion despite a lack to detect donor chimerism. In addition, in the limited number of patients evaluated the administration of fludarabine prior to CTLs infusion enhanced the clinical responses observed. While clinical effects had been observed in HL

patients treated with EBV-specific CTLs, the anti-tumor effects are not as robust as what has been observed in patients with PTLDs. Several observations can account for such differences, EBV infected HRS usually express less immunogenic EBV proteins in contrast to PTLD patients (LMP2). In addition, HRS cell have mechanisms to evade immune response to EBV infection including down-regulation of the immunogenicity of latent EBV antigen (i.e. LMP2) and secretion of the immunosuppressive cytokines such as IL10, IL-13, TARC, TRAFs (tumor necrosis factor receptor-associated factors) and TGFβ which may suppress the efficacy of EBV specific CTL.[93-95] Using the strategies to enhance Th1 CTLs development and decrease Th2 cytokine production may overcome the defective immune recognition of HRS cells and improve the efficacy of the EBV specific CTL therapy in rel/ref HL (Table 5).

Clinical trial	Agent	Study design	Patient population	Clinical outcome	N	Location
NCT00058617	Autologous EBV Specific CTLs	Phase I	EBV positive HL, NHL, Plasma cell neoplasm	Safety, immunological efficacy and anti-tumor effects	N=18	Baylor College of Medicine
NCT01192464	Autologous Chimeric Receptors CD30 (CARCD30) + EBV Specific CTLs	Phase I	Rel CD30+ HL, NHL or newly diagnosed but unable to receive standard therapy CD30+ HL or CD30 + NHL with plan for high dose therapy and ASCT	Safety and anti-tumor effects of CARCD30 EBV Specific CTLs	N=18	Baylor College of Medicine
NCT00082225	Autologous/synergeic/allogeneic LMP2a Specific CTLs following anti-CD45 antibody	Phase I	Rel EBV positive HL or NHL	Safety and anti-tumor effects	N=4	Baylor College of Medicine
NCT00062868	Autologous/allogeneic LMP Specific CTLs	Phase I	Rel EBV positive HL or NHL	Safety and anti-tumor effects	N=108	Baylor College of Medicine
NCT00368082	Autologous/syngeneic/ allogeneic TGFβ resistant LMP Specific CTLs	Phase I	Rel EBV positive lymphomas	Safety and anti-tumor effects	N=20	Baylor College of Medicine
NCT00608478	Autologous LMP1 and LMP2 Specific CTLs plus antiCD45 antibody	Phase I	Rel EBV positive lymphomas	Safety and anti-tumor effects	N=24	Baylor College of Medicine

N= number of patients; HL = Hodgkin Lymphoma; NHL = Non-Hodgkin lymphoma; Rel/ref = relapsed/refractory; EBV = Epstein Barr Virus; CTL = cytotoxic T-cell lymphocytes; LMP = Latent membrane protein; LMP2a = Latent membrane protein 2a.

Table 5. Ongoing trials of EBV-Specific CTLs for patients with relapsed/refractory Hodgkin lymphoma.

6.3 Allogeneic bone marrow transplant (AlloSCT)

Approximately 50% of patients with relapsed Hodgkin lymphoma who undergo HDC-ASCT relapse as a consequence of refractory disease, usually within the first year post-transplant.[96,97] Relapsed HL patients after HDC-ASCT have a poor clinical outcome and represent a therapeutic challenge for the practicing oncologist. There are several proposed risk factors to identify patients at high risk to develop disease progression following HDC-ASCT such as chemotherapy resistant disease prior to HDC-ASCT, B symptoms at the time of relapse, residual disease at the time of transplantation by functional imaging, extra-nodal disease at the time of relapse, and bulky disease.[98,99] Patients with any of these high risk factors may be suited for alternative therapeutic strategies such as tandem transplant, allogeneic bone marrow transplant, and/or post-HDC-ASCT maintenance therapy in the context of a clinical trial.

A second HDC-ASCT could be considered for patients with a long period of remission following the initial transplant (>3 years) or those whom alloSCT is not feasible.[100]

AlloSCT has been used in patients with rel/ref HL with controversial results. Often the high incidence of transplant related mortality (TRM) offsets the potential clinical benefit.[101] While the incorporation of reduced intensity conditioning regimens has been associated with lower TRM rates, the long-term PFS rates rarely exceed 20-25% questioning the validity of this approach. Patients who have chemotherapy sensitive disease, non-bulky disease, and have greater than 1 year of remission after the first HDC-ASCT seem to have most benefited with this approach.[102]

Despite early good responses, the results of RIC-AlloSCT demonstrate a disappointing clinical outcome and lack of long term disease control with 2 year OS of 29-66% and 2 year PFS of 20-39% regardless of conditioning regimens or donor types.[103-105] Peggs et al reported durable response to donor lymphocyte infusion (DLI) in patients with relapsed HL post alloSCT that incorporated *in vivo* T-cell depletion.[106] DLI was administered to 46 patients for mixed chimerism (n=22) and relapsed disease post-alloSCT (n=24). Eighty-six percent of patients with mixed chimerism converted to full donor status and had a 4-year relapse incidence of 5%. More importantly, CR and PR were noted in 58.3% and 20.8% of 24 patients with relapsed disease respectively, suggesting the existence of graft vs. HL effects. Ongoing clinical studies are investigating the role of alloSCT in relapsed HL patients with poor-risk features who are at high risk to relapse after HDC-ASCT.

In summary, promising therapies are emerging for the treatment of rel/ref HL. Substantial and occasionally durable remissions have been observed with some therapeutic interventions, such as HDACi, drug immunoconjugates, and cellular therapy. Ongoing studies will hopefully guide the integration of these therapies in the current treatment of high-risk HL in an attempt to improve cure rates. In addition, ongoing scientific and translational research and the importance of the development of novel therapeutics for patients with ref/rel HL should not be underemphasized.

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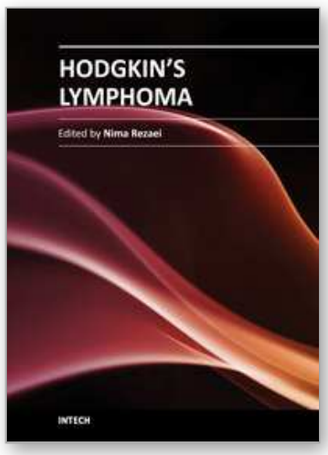

Hodgkin's Lymphoma
Edited by Dr. Nima Rezaei

ISBN 978-953-51-0402-5
Hard cover, 272 pages
Publisher InTech
Published online 23, March, 2012
Published in print edition March, 2012

Hodgkin's Lymphoma is the book consisting of 11 chapters: Recent insights into the biology of Hodgkin's lymphoma, including historical aspects, epidemiology, pathophysiology, genetic defects, and prognostic indicators are explained in the intro chapters. After a translational chapter from tumor microenvironment to immunotherapeutic approach, treatment of early stage, advanced, and refractory Hodgkin's lymphoma are explained in the following chapters. MALT lymphoma and adverse effects of chemotherapy and radiotherapy in the affected patients are discussed in the subsequent chapters, while the final chapter is focused on survivorship in Hodgkin's lymphoma. The book is intended to present recent advances in the pathophysiology of Hodgkin's lymphoma as well as practical approach to diagnosis and management in clinical practice, which is hoped to be welcomed by the physicians, who wish to learn more about Hodgkin's lymphoma.

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