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Customized Targeted Therapy in Hodgkin Lymphoma: Hype or Hope?

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Synopsis

Although the majority of patients with Hodgkin lymphoma (HL) are cured with primary therapy, patients with primary refractory disease or relapse after initial treatment have poor outcomes and represent an unmet medical need. Recent advances in unraveling the biology of HL have yielded a plethora of novel targeted therapies. This review provides an overview of the data behind the hype generated by these advances and addresses the question of whether or not clinically these targeted therapies offer hope for patients with HL.

Keywords

Hodgkin lymphoma; relapsed disease; targeted therapies; brentuximab vedotin

Introduction

Classical Hodgkin lymphoma (HL) represents ~ 10% of all lymphomas diagnosed annually in the developing world. In 2013, approximately 9000 cases of HL were diagnosed in the US [1]. With a median age of 38 years, and at least 40% of patients under age 35 at the time of diagnosis, it is the most common lymphoma affecting young patients [2]. Over the past 30 years valuable lessons learnt about late effects of therapy, specifically cardiovascular and second cancer risk, have led to treatment modifications of radiation dose and field size as well as alkylator exposure, which have led to significant risk reduction of competing causes

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of death [3–5]. As a result of these advances more than 75% of patients are cured with contemporary frontline therapy [6,7].

For patients who relapse after attaining an initial complete remission (CR), or have primary refractory disease, the standard treatment approach is salvage chemotherapy followed by autologous stem cell transplant (ASCT) with ~ 50% cure rate [8]. Several studies show that achieving a CR prior to ASCT is one of the most important factors in determining long-term outcome post ASCT [9,10]. Other pre-transplant prognostic factors include: duration of initial remission, extent of disease at relapse, and constitutional symptoms [11–14]. In an international collaborative effort from 5 countries, data on 756 patients with relapsed HL with a minimum of 1 year follow-up post-transplant were pooled [15]. The overall median post-progression survival (PPS) for patients relapsing after ASCT was 1.3 years. Seventy-one percent of relapses occurred within 1 year after ASCT, and were roughly equally distributed in the periods: <3 months (22%), >3 and <6 months (22%), and >6 and <12 months (27%). The median PPS for these periods were 0.55, 1.6, 1.68, and 2.26 years for time to relapse after ASCT respectively ($p<0.0001$). [15]. Allogeneic stem cell transplantation (alloSCT) can induce durable remissions in some of these patients; however its utility is limited by the challenges of finding an available stem cell donor, and achieving adequate disease control prior to transplantation [16]. Therefore novel treatments to increase the CR rate pre SCT, or significantly prolong remission duration post SCT, have been sought.

The recent approval in 2011 of brentuximab vedotin, an antibody drug conjugate (ADC) targeting CD30, has been the first major advance in the management of HL after several decades and offers considerable hope to patients with refractory disease or relapse after SCT [17]. Better understanding of the biology of HL has led to exploration of several other potential targets as therapeutic options. This review provides an overview of HL tumor biology in the context of the development of novel targeted therapies. We discuss four broad categories of targeted therapies either approved or under investigation: 1) therapies targeting HRS cell surface receptors, 2) therapies targeting reactive immune cells in the tumor microenvironment, 3) adoptive immunotherapy, and 4) therapies targeting signaling and intracellular survival pathways (Tables 1 and 2). While some of the agents discussed below are highly active as single agents, many others demonstrate modest single agent activity. Moving forward the challenge will be how to develop rational combinations of these novel agents within the context of current paradigms of care to achieve enhanced efficacy with minimal toxicity.

Emerging Targets in the Biology of Hodgkin Lymphoma

Classical HL is a B cell lymphoid neoplasm, characterized by Hodgkin Reed Sternberg (HRS) cells. The malignant HRS cells represent only a small fraction (0.1–1,0%) of the total cellular population and exist within an inflammatory microenvironment that supports tumor growth and suppresses immune surveillance [18–22]. HRS cells grow poorly both *in vitro* and *in vivo* murine models without microenvironment support, underscoring its role in HL growth and survival [19,23]. The cross talk between the HRS cells, the peritumoral cells in the tumor microenvironment, and secreted cytokines, propagates HRS cell growth, proliferation, and evasion of immune regulation.

HRS cells express many surface receptors including CD15, CD30 CD40, CD80, and CD25 (the alpha chain of the IL-2 receptor)[24]. Additionally up-regulation of the programmed death ligand-1 (PDL-1) on HRS cells induces anergy in peritumoral T cells, which themselves express PD-1. High expression of PD-1 by peritumoral lymphocytes has been reported to be an independent predictor of inferior overall survival (OS) [25,26]. Galectin-1 (gal-1) expression inhibits infiltration of CD8+ effector cells, expression of TNF-related apoptosis inducing ligand (TRAIL), and Fas ligand induced apoptosis of cytotoxic T lymphocytes (CTLs) [27,28]. HRS cells further shape their microenvironment by secreting immunosuppressive cytokines and chemokines, such as the chemokine thymus and activation-regulated chemokine/CCL17 (TARC), CCL5, and CCL22. These in turn, attract T helper 2 (Th2) and regulatory T (Treg) cells to the tumor microenvironment, as well as interleukin-7 (IL-7), which then induce differentiation of naïve CD4+ T cells towards FoxP3+ Treg cells [29–31]. In fact, high serum levels of the chemokine TARC at diagnosis have been associated with an inferior clinical outcome [32]. Tumor associated macrophages (TAM) induce signal transducer and activator of transcription (STAT) mediated suppression of T cell surveillance and cell directed cytotoxicity. Increased numbers of CD68 and CD163 expressing TAMs are also associated with inferior survival in newly diagnosed HL patients treated with standard therapy, as well as in patients following ASCT [33]. Cumulatively the tumor microenvironment induces T cell exhaustion and deficient anti-tumor immunity, which plays a key role in propagating a permissive milieu for HL growth. While many of the dots of this complex network have been connected, it is still unclear how they all fit together or what is the logical road map for treating relapsed and refractory HL. At a conceptual level targeted therapies can be broadly classified as targeting: 1) HRS cell surface receptors, 2) the tumor microenvironment, 3) cell-mediated immunity (adoptive immunotherapy) and 4) signalling pathways. Figure 1 displays selected novel agents in the context of their targets.

Targeting Molecules Expressed on HRS Cell Surface

Receptors highly expressed on the HRS cell surface, with low to absent expression on normal tissues, are optimal for targeted therapy. Trials evaluating these targets are summarized in Table 1 and 2.

Targeting CD30

CD30 is highly expressed on HRS cells, and nearly absent on normal tissue, making it an optimal target of directed therapy. It is a 120-KDa type I transmembrane glycoprotein belonging to the tumor necrosis factor (TNF) superfamily and induces signaling pathways that promote HRS cell proliferation [34]. The most successful targeted therapy developed to date in HL has been brentuximab vedotin, an ADC directed against the CD30 receptor. Early clinical studies targeting CD30 with naked antibodies SGN-30 (cAC10), and MDX-060 did not demonstrate meaningful anti-tumor activity largely attributed to suboptimal antigen binding, and neutralization of anti CD30 antibodies by soluble CD30 [35–37]. In an effort to increase cytotoxicity, a valine–citrulline peptide linker to monomethyl auristatin E (MMAE), a synthetic analogue of the naturally occurring antimitotic agent dolastatin 10, was added to the chimeric antibody cAC10 (SGN-30) creating the ADC brentuximab vedotin. Robust anti-tumor activity reported in two phase I

clinical trials led to a lot of hype regarding this agent [38,39]. These data were subsequently confirmed in a phase II pivotal trial of 102 patients with heavily pretreated HL who had relapsed after ASCT [17]. Overall treatment was well tolerated and ≥ grade 3 events or dose limiting toxicities (DLT) included neutropenia (20%), thrombocytopenia (8%), peripheral sensory neuropathy (8%) and anemia (6%). The response rate in this heavily pre-treated population was striking with an overall response rate (ORR) of 75%, and a CR rate of 34%. The median progression free survival (PFS) was 5.6 months, with a median duration of response (DOR) of 20.5 months [17].

These compelling data, led to FDA approval of brentuximab vedotin in 2011 for patients with relapsed/refractory HL who have failed ASCT, or two chemotherapy regimens. Data also suggest that brentuximab vedotin is active as a retreatment strategy with an ORR of 57% [40]. Recently, two retrospective analyses suggest that brentuximab vedotin also provides a potential bridge to successful alloSCT [41,42]. The combination of brentuximab vedotin with donor lymphocyte infusion has been shown to induce both anti-tumor immunity and sustained clinical responses in 4 patients with early relapse post alloSCT [43]. Ongoing trials are evaluating brentuximab vedotin as a maintenance strategy for high risk patients after ASCT, and for relapsed disease in combination with chemotherapy or immune based therapies such as ipilimumab (Table 2).

The development and subsequent approval of brentuximab vedotin is a clear example of a novel therapy that has moved well beyond hype and offers hope for patients with relapsed and refractory HL. As a logical next step, trials evaluating its role in the frontline setting are ongoing (Tables 1 and 2). Preliminary results of a phase I trial evaluating the combination of brentuximab with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) has been reported [44]. Unfortunately, 44% (11/25) of patients experienced significant pulmonary toxicity, including two deaths on study. Subsequently with modification to exclude bleomycin (AVD), 7 of the 11 patients completed treatment without further toxicity. Notably, no pulmonary toxicity was observed in an expanded AVD-brentuximab cohort and preliminary results report a PET/CT CR of 96% [44]. These data have led to a phase III frontline trial for patients with untreated advanced HL evaluating the activity of ABVD versus brentuximab-AVD. Other frontline trials include a phase I trial of ABVD followed by 6 cycles of brentuximab vedotin for patients with untreated stage I and II non-bulky HL, and a randomized trial of brentuximab vedotin in combination with etoposide, cyclophosphamide, adriamcyin, procarbazine, prednisone and brentuximab (ECAPP B) versus etoposide, cyclophosphamide, adriamcyin, doxorubicin, dacarbazine and brentuximab (ECADD B) in patients with high risk advanced stage HL. These combinations of brentuximab vedotin with standard therapy or other targeted agents continue to offer hope that in the future there may be novel treatment platforms which are well tolerated with possibly superior activity.

Other Cell Surface Targets

CD80 is a costimulatory molecule highly expressed on HRS cells and inhibits antigen-specific T cell lymphoproliferation and interferon-gamma secretion [45]. Galiximab, a primatized IgG1 monoclonal antibody against CD80, has high affinity binding for CD80,

and induces antibody dependent cytotoxicity (ADCC) [46]. In a phase II clinical trial in patients with relapsed and refractory HL galiximab was well tolerated but had disappointing activity, with an ORR of 6.9% and a median time to progression (TTP) of 1.6 months [46,47].

CD40 is widely expressed on B and T cells and a member of the tumor necrosis factor receptor (TNFR) family which induces cell proliferation, survival, secretion of cytokines, and activation of both the classical (canonical) and alternative (non-canonical) pathways of nuclear factor Kappa B (NFκB) signaling [48]. Lucatumumab (HCD122) targets both CD40+ HRS cells, and Th2/Treg signaling and has been investigated in HL (59). A phase II trial reported an ORR of 16%, all partial responses (PRs) in 18 patients with relapsed/ refractory HL [49]. The therapy was generally well tolerated and reversible asymptomatic hepatotoxicity was the primary DLT.

Agents that have been investigated but are not currently in development include antibodies to the TRAIL protein, and CD25, the alpha chain of the IL-2 receptor. A phase I trial of the TRAIL-R2 antibody AMG655 in combination with bortezomib or vorinostat was suspended due to poor patient accrual. A clinical trial of the anti CD25 immunotoxin RFT5-SPMT-dgA had significant toxicity due to vascular leak syndrome and disappointing results, with only 13% of patients achieving a PR [50]. A monoclonal antibody targeting IL-13 (TNX-650) is currently under investigation, however to date no clinical data have been reported.

In summary, while there has been considerable hype based on the biologic rationale of using antibodies to target differentially expressed cell surface receptors, none have matched the efficacy of brentuximab vedotin. More insightful science and combination strategies are required to truly translate to hope in the clinical setting.

Targeting the Tumor Microenvironment

Monotherapies targeting only the HRS cells are limited in their efficacy due to the major role of the microenvironment in regulating HRS function and survival [19].

Strategies targeting tumor-microenvironment interactions aim to disrupt its cellular components, or activate peritumoral T and NK cells to induce anti-tumor responses. Encouraging pre-clinical data of agents in development include: immunomodulatory drugs (lenalidomide) monoclonal antibody directed targeting of peritumoral CD20+ B cells (rituximab, almentuzumab), bispecific antibodies, such as AFM13 which simultaneously targets CD30 bearing HRS cells and CD16 on natural killer cells, selective inhibition of colony-stimulating factor-1 (CSF1R) a growth factor for tumor-associated macrophages (TAMs), the anti-CTLA-4 antibody ipilimumab, and the checkpoint inhibitors targeting PD-1 and anti-PDL-1 [51,52]. Ongoing trials are outlined in Table 2.

Lenalidomide is an immunomodulatory and anti-angiogenic agent, with a putative mechanism of activating cytotoxic T lymphocytes (CTLs) and NK cells against HRS cells [53]. The safety and efficacy of lenalidomide as a monotherapy has been investigated in several studies. In a multicenter phase II study, 36 patients with relapsed HL were treated with 25 mg/day of lenalidomide on days 1–21 of a 28 day cycle. The ORR was 19% with moderate grade 3–4 hematologic toxicity noted;neutropenia (47%), leukopenia (29%),

anemia (26%), and thrombocytopenia (18%) [54]. A smaller study of 15 patients reported similar results for toxicity, as well as efficacy with an ORR of 13%. Seven additional patients had stable disease. The median TTP was 3.2 months[55]. Cumulatively, these studies suggest that lenalidomide has modest single agent activity in relapsed HL. There is hope that efficacy may be enhanced by combinations with chemotherapy or other HRS targeting agents with trials ongoing (Table 2).

AFM13, a bispecific tetravalent human antibody construct that simultaneously targets CD30 and CD16 on natural killer (NK cells), has been evaluated in a phase I clinical trial in relapsed/refractory HL. Patients were heavily pretreated with a median of 6 (range 3 –11) prior therapies. Of the 28 patients enrolled, 9 had received previous brentuximab vedotin, and 14 were refractory to prior therapy. AFM13 was safe and well tolerated. The most frequent adverse events included: infusion-related reactions (headache, fever, fatigue and myalgia) in 33% of patients. Moderate clinical activity (2 patients achieved PRs, 14 patients SD) was demonstrated and more mature follow-up is needed to discern potential [56].

While HRS cells rarely express CD20, the tumor microenvironment is rich in CD20 expressing B cells, and a study suggests that circulating clonotypic B cells may be the HL tumor initiating cells [57]. Some studies suggest that these B cells deliver survival signals to HRS cells, and suppress T cell activation via IL-10 production [58]. In contrast, other studies report that the presence of CD20 expressing B cells in the tumor microenvironment is associated with improved survival [59,60]. Nonetheless, targeting CD20 with the monoclonal antibody rituximab has been actively investigated. In a pilot study 22 patients with relapsed/refractory HL were treated with single agent rituximab. The ORR was 22% and included PRs, as well as CRs [61]. Interestingly, 6 of 7 patients with CD20 negative HRS cells experienced resolution of B symptoms, suggesting a possible role for CD20+ B cells in mediating the systemic cytokine response [61]. Therefore it is unclear whether the activity of rituximab is due to a direct effect on HRS cells (that are occasionally CD20-positive), or a depletion of supporting B cells and peritumoral CD20+ cells. These encouraging single agent data provided the rationale to investigate rituximab in combination with chemotherapy. The safety and efficacy of rituximab and gemcitabine was investigated in 33 patients with relapsed HL. The ORR was 48% independent of HRS cell CD20 expression; however, the median failure free survival (FFS) was only 2.7 months [62]. Two phase II trials have evaluated rituximab in combination with ABVD. In the first trial, 78 patients with newly diagnosed HL were treated with weekly rituximab for 6 weeks, and standard ABVD for 6 cycles [63]. The combination was well tolerated with neutropenia, fatigue, and nausea the most frequent treatment related adverse events. At 68 months the event free survival (EFS) and OS, were 83% and 96% respectively. These results were superior to ABVD alone when compared to institutional historical data. A second phase II study reported similar results with a 3 year EFS and OS of 83% and 98% respectively [64]. Interestingly, in this study circulating clonotypic B cells were associated with a greater frequency of relapse. Other ongoing studies are evaluating the contribution of rituximab to first line augmented bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) for patients with advanced untreated HL (HD18), and in combination with ABVD as frontline therapy for patients with advanced stage poor risk HL (Table 2).

In summary while there is reasonable hype about the rationale to target CD20, results of randomized controlled trials are required before the question of hype versus hope can be definitively answered.

CD52 is another cell surface receptor highly expressed on peritumoral B cells. Almentuzumab a humanized monoclonal anti-CD52 antibody binds to CD52 purportedly inducing cell lysis via antibody dependent cell-mediated cytotoxicity (ADCC) [65]. A phase II study investigating the efficacy of single agent almentuzumab in relapsed/refractory HL was terminated due to slow patient accrual, and data has not been reported to date. The efficacy of the combination of almentuzumab with etoposide, prednisone, vincristine, cyclophosphamide, and adriamycin (EPOCH) chemotherapy in relapsed/refractory HL is currently under investigation (Table 2).

Direct immune based approaches, which reverse the anergy of peritumoral T cells and stimulate anti-tumor cytolytic activity, represent another novel strategy against relapsed/ refractory HL. The association of high expression of TAMs with a short PFS, led to significant hype for evaluating their inhibition with compound PLX3397, a selective inhibitor of CSF1R (a growth factor for TAMs). Unfortunately, despite the inhibition of both CSF1R and Kit, in a phase II trial of 20 heavily pretreated HL patients PLX3397 had only modest activity, with an ORR of 5% and a median PFS of 56 days [66]. Therefore the role of CSF1R in HL lymphoma biology needs to be better understood before these strategies move from hype into hope.

Lastly, immune activating strategies such as the combination of the anti-CTLA-4 antibody (ipilimumab) with brentuximab vedotin, and the anti-CD27 antibody (CDX1127) are being investigated. Checkpoint inhibitors against PD-1 expressed on peritumoral T cells, or PDL-1 expressed on HRS cell surface are also undergoing active investigation (Table 2).

In summary, it is too early in development to discern whether the data from agents targeting reactive immune cells in the tumor microenvironment, as summarized in this section, will translate to hope. Results of ongoing clinical trials over the next few years will help shed some light on the efficacy of these agents both in terms of a response rate and durability.

Adoptive Immunotherapy in HL

Adoptive immunotherapy allows the generation and transfer of T cells engineered *ex vivo* to target and attack tumor cells in the host, as well as immune activation of the tumor microenvironment. In relapsed/refractory Epstein Barr virus positive (EBV+) HL, an adoptive approach using *ex vivo* expansion of viral EBV antigen specific CTLs produced striking results albeit in a small number of patients [67,68]. In this pilot study, 83% (5 of 6) patients with relapsed EBV+ HL had a clinical response, of which 4 achieved CRs sustained for more than 9 months. Other trials of adoptive immunotherapy, i.e. targeting EBV-HL through MAGE antigen, or genetically engineered T lymphocytes expressing a chimeric CD30 antigen receptor, are ongoing but have not reported data to date [69,70]. Only time will tell if these innovative strategies will constitute a new domain of hope or not.

Targeting Downstream Signaling and Intracellular Survival Pathways

Several drugs target constitutively activated downstream signaling pathways that drive HRS cell proliferation, and enhance tumor cell survival. Epigenetic changes in HRS cells modulate B cell silencing, immune escape, and the transcription of genes underlying cell proliferation and survival [71]. The acetylation state of proteins are modified by the opposing effects of both histone acetyltransferases (HATs) and histone deacetylases (HDACs). There are currently 4 classes of HDACs: classes I and IV are constitutive nuclear proteins that regulate cell proliferation, class II HDACS regulate genes that promote cell growth and shuttle between the nucleus and the cytoplasm, and class III HDACSs regulate chromatin structure [72]. Increased expression of HDACs relative to normal tissues has been observed in HL, and in at least one study correlated with poor treatment outcome [73].

Histone deacetylase inhibitors (HDACI) modulate cellular processes and signaling pathways that are dysregulated in cancers [74,75]. HDACI target tumor cells and their interaction with their local microenvironment through multiple epigenetic mechanisms including chromatin condensation and acetylation of histones affecting gene expression. Treatment of HL patients with HDACI decreases the secretion of the inhibitory cytokine CCL17 (TARC) *in vitro* [76]. Currently, two broad classes of HDACIs are under investigation in HL: pan HDAC inhibitors that inhibit HDAC class I and II (i.e. vorinostat, and panobinostat), and selective HDACIs that preferentially inhibit class I HDACs (mocetinostat and etinostat).

Vorinostat, mocetionostat, and panobinostat have been investigated as monotherapies in relapsed/refractory HL. In a phase II study of oral vorinostat the ORR was only 4% [77]. More promising reports have been reported for panibinostat in a phase II trial of 129 HL patients, all of whom had failed ASCT. The primary toxicities were hematologic. Grade 3–4 toxicities included 79% thrombocytopenia (79%), 21% anemia (21%) and neutropenia (21%). The ORR in this heavily pre-treated patient population was 27% (23% PR, 4% CR), with a median DOR of 6.9 months, and an estimated 1-year OS rate of 78%. The median PFS was ~ 6 months and 52 patients (40%) had PFS greater than 24 weeks [78]. Responses were associated with a decrease in serum Tarc levels [78,79].

Mocetinostat has been evaluated in a phase 2 trial in relapsed/refractory HL. Significant toxicity was seen at the 110mg dose including grade ≥ 3 myelosuppression, fatigue, pneumonia, and in 4 patients pleural effusions (3 ≥ grade 3). The drug was better tolerated at the reduced dose of 85mg with an ORR of 21% [80].

Cumulatively, these data suggest that HDACI have activity, however the hematologic toxicity profile will likely make combination strategies with chemotherapy challenging. Currently the optimal HDACI strategy to move these drugs from the hype category to the hope category remains unclear.

HRS cells constitutively express NF-κB, in part as a result of somatic mutations in pathway members and regulators, as well as other anti-apoptotic proteins, which inhibit both the intrinsic and extrinsic pathways of apoptosis [21,23]. Bortezomib, a reversible proteasome inhibitor of NFκB signaling, enhances apoptosis through down regulation of the anti-apoptotic molecules XIAP and c-FLIP and has a putative role as a chemotherapy sensitizing

agent [81]. Although bortezomib demonstrated anti-proliferative activity *in vitro*, a phase II clinical trial in relapsed/refractory HL failed to demonstrate meaningful clinical activity [82]. The evidence for synergy between cytotoxic chemotherapy and bortezomib in non-Hodgkin lymphoma led to the evaluation of the combination of bortezomib and chemotherapy in relapsed/refractory HL. In a phase I trial of ifosfamide, carboplatinum and etoposide (ICE) in combination with bortezomib (BICE) given on days 1 and 4 of standard infusion, the ORR for 12 patients was 69% but significant myelosuppression was seen [83]. A second study combined bortezomib given twice weekly (days 1, 4, 8, 11) in a 3 week cycle at a dose of 1 mg/m^2 with gemcitabine $800mg/m^2$ on days 1 and 8. This combination had significantly lower activity (ORR 22%) with higher toxicity (grade 3 transaminitis) than the BICE treated patients, and was not pursued further. A study targeting NFκB with MLN4924, a small molecule inhibitor of neddylation 8, has recently been terminated due to slow accrual, and no data has been reported to date.

Other constitutively activated pathways in HRS cells include: Janus kinase-signal transducer and activator of transcription (JAK-STAT), and the phosphatidyliositol 3-kinase pathway (PI3K/AKT/mammalian target of rapamycin (MTOR) pathway). Inhibitors of JAK2 inhibitors suppress STAT phosphorylation in HL cells lines, and downregulate the expression of PDL-1 *in vitro* [84], however a phase I trial of the JAK2 inhibitor SB1518 did not have significant clinical activity, despite a tolerable safety profile [85].

Inhibition of MTOR has a myriad of *in vitro* effects including enhancement of apoptosis, cell cycle arrest, and autophagy [86,87]. The clinical activity of the MTOR inhibitor everolimus was evaluated in a phase II trial in patients with relapsed/refractory HL. The ORR of this heavily pretreated patient population was 47%, with 8 patients achieving a PR, and one a CR. The median TTP was 7.2 months, with 4 responders remaining progression free at 12 months [88]. Overall the therapy was reasonably well tolerated except in four patients who experienced grade ≥ 3 pulmonary toxicity. A synergy between targeting MTOR and other inhibitors of downstream signaling, such as PI3K and HDAC, has been suggested by *in vitro* data, and this combination is currently being evaluated. In a phase I/II study of the combination of everolimus with the HDACI panobinostat, the ORR for 13 HL patients was 46% [89]. Combinations of everolimus with immunomodulatory agents, such as lenalidomide, as well as with PI3K inhibitors are currently under investigation.

Conclusion

Advances in HL biology over the past few years have yielded a plethora of novel targets and an unprecedented opportunity to develop newer therapies. These targeted therapies offer the potential to increase cure rates in patients with relapsed and refractory HL, along with the hope of decreasing long-term toxicity. The approval of brentuximab vedotin clearly offers new hope to patients with relapsed and refractory disease, and may have promise as frontline therapy. Currently there are many novel targeted therapies under clinical investigation in HL, and many more waiting to move from bench to bedside. Although these advances are exciting, it is unlikely that one size will fit all, or that any single therapy or therapeutic platform will be curative for all patients. The challenges ahead are to identify strategies that offer maximal tumor eradication with minimal systemic toxicity, and to identify subsets of

patients with the highest likelihood of efficacy to a particular therapy. To accomplish this, more robust methods of risk stratification incorporating both clinical and biologic factors to identify patients at the highest risk of therapy failure are needed. This gap needs to be addressed before the full potential of novel targeted therapies can be realized and the hope of customized targeted therapies will then surpass the hype.

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Key Points

- HL patients with primary refractory disease or relapse after transplant have poor outcomes and represent an unmet need.
- Therapies derived from an understanding of HL biology can be broadly classified as targeting: the Hodgkin Reed Sternberg cell surface receptors, tumor microenvironment, cell mediated immunity, and intracellular signaling pathways.
- Brentuximab vedotin, an antibody-drug conjugate targeting CD30, now FDA approved, offers substantial hope for improving outcomes in the treatment of HL.
- Other therapies in development need longer follow-up to realize their potential.

Objectives

1. Review recent advances in HL biology
2. Review development of novel targeted therapies in the context of HL biology
3. Review results of clinical trials with targeted therapies

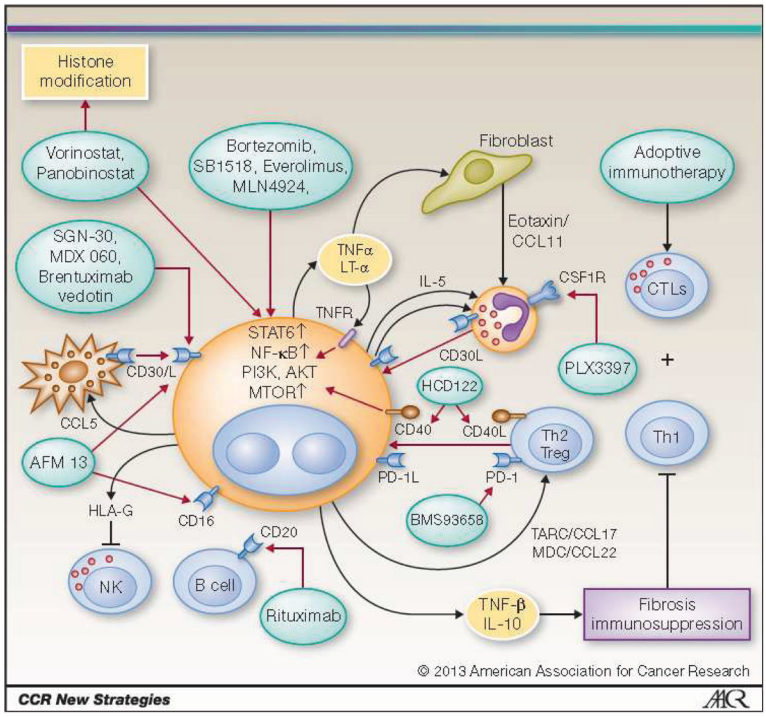

Figure 1.
Selected Novel Agents in the Context of the Biological Targets

Table 1

Current Results in Selected Targeted Therapies in HL

DRUG/PHASE	MAIN TARGET	CLINICAL TRIAL NUMBER	FAILED ASCT (%)	CLINICAL RESULTS	REFERENCE
RECEPTOR TARGETED THERAPIES					
1) SGN-30 (I) 2) SGN-30 (II)	CD 30+ HRS Cells	1) NCT00051597 2) NCT00337194	83[a] 68	No significant response	35–37
MDX-060 (1/2)	CD 30+ HRS cells	NCT00284804	87[a]	No significant response	35–37
Brentuximab Vedotin (BV) 1) BV/(I) 2) BV/(I) 3) BV/(II)	CD 30+ HRS cells	1) NCT00947856 2) NCT01100502 3) NCT01060904	73[a] 68[a] 100	PIVOTAL Trial: ORR 75%, CR 34%, median PFS 5.6 mos, median DOR 20.5 mos	17,38,39
HCD122 (II)	CD40+ HRS cells; Th2/Treg signaling	NCT00670592	NR	ORR 16% (all PR)	49
Galiximab (II)	CD80+ HRS cells	NCT00516217	83	ORR of 6.9%, TTP 1.6 months	46,47
MICROENVIRONMENT TARGETING					
Lenalidomide (II) Lenalidomide (II)	Immunomodulation, anti- angiogenesis	1) NCT00540007 2) NCT00478959	76 67	1) ORR 19% (N = 32) 2) ORR 13% (N = 15)	54,55
AFM 13 (I)	CD 16/30+ HRS cells	NCT01221571	NR	7% PR / 50% SD	56
1) Rituximab single agent (I Pilot) 2) Rituximab + Gemcitibine (II) 3) A) Rituximab + ABVD frontline (I) B) Rituximab + ABVD frontline (II)	CD20+ peritumoral B lymphocytes; CD20+ HRS cells	3A) NCT00504504 3B) NCT00369681	82 55 0 0	1) ORR 22%, median DOR 8.7 mos 2) ORR 48%, median FFS 2.7 mos 3A) EFS 83% and OS 96% 3B) EFS 83% and OS 98%	61626364
PLX3397 (II)	CSF1R inhibitor	NCT01217229	NR	ORR 5%	66
ADOPTIVE IMMUNOTHERAPY					
Epstein-Bar virus positive specific cytotoxic T-cells	EBV+ HRS cells	NCT00058617[a]	40	83% of 28 patients with EBV+ HL had a clinical response, including 4 CRs sustained >9 mos	67,68
DOWNSTREAM SIGNALING PATHWAY					
Panobinostat (I)	Histone modification	NCT00742027	100	ORR 27% including 4% CR, median PFS was 6.1 mos	78
Vorinostat (I)	Histone modification, STAT signaling (pSTAT6)	NCT00132028	44	ORR 4%	77

DRUG/PHASE	MAIN TARGET	CLINICAL TRIAL NUMBER	FAILED ASCT (%)	CLINICAL RESULTS	REFERENCE
Mocetinostat (I)	Histone modification, STAT signaling	NCT00358982	84	ORR 21%	[80]
Everolimus (I)	PI3K signaling, mTOR, TNFR signaling	NCT01022996	84%	ORR 47%. 8 PR, 1 CR. Median TTP 7.2 months, 4 responders remained progression free at 12 mos	[88]
SB1518	JAK/STAT pathway	NCT01263899	NR	No significant clinical activity	[85]

*All Trials are in Relapsed/Refractory Patients Unless Otherwise Indicated

[a]Includes patients with HL and NHL;

NR: not reported; NA: not available, ORR: overall response rate; CR: complete response; PR: partial response, PFS: progression free survival; TTP: time to progression; DOR: duration of response ASCT: autologous stem cell transplant; mos: months

Table 2

Selected Ongoing Clinical Trials of Novel Agents

DRUG	MAIN TARGET	CLINICAL TRIAL NUMBER
RECEPTOR TARGETED THERAPIES		
Brentuximab vedotin (BV) combinations		
Frontline	CD 30+ HRS cells	
1) Phase 3 frontline with AVD versus brentuximab/AVD		1) NCT01712490
2) ECAPPB vs. ECADD B (frontline)		2) NCT01569204
Relapsed/Refractory		
3) ABVD → BV (relapsed)		3) NCT01578967
4) BV+ Bendamustine (relapsed)		4) NCT01874054
5) BV+ Ipilimumab (relapsed)		5) NCT01896999
6) BV vs. ICE pre ASCT (relapsed)		6) NCT01393717
7) BV → ICE (relapsed)		7) NCT01508312
8) BV + Rituximab (relapsed)		8) NCT01900496
Maintenance		
9) BV Maintenance after ASCT (ATHERA) (maintenance)		9) NCT01620229
TNX-650	IL-13	NCT00441818
MICROENVIRONMENT TARGETING		
Lenalidomide Combinations (relapsed)		
1) AVD	Immunomodulation, anti-angiogenesis	1) NCT0105667
2) Bendamustine,		2) NCT01412307
3) Romidepsin		3) NCT01742793
4) Everolimus		4) NCT01075321
Rituximab Combinations		
Frontline	CD20+ peritumoral B lymphocytes; CD20+ HRS cells	
1) Rituximab ABVD vs. ABVD Phase 2		1) NCT00654732
2) Rituximab + BEACOPP (HD18)		2) NCT00515554
Relapsed		

DRUG	MAIN TARGET	CLINICAL TRIAL NUMBER
3) Rituximab + Bendamustine		3) NCT01900496
Ipilimumab (relapsed)	Immunomodulation of tumor microenvironment	NCT01896999
Nivolumumab[a] (relapsed)	PD-1 expressing peritumoral lymphocytes	NCT01592370
CDX1127 (relapsed)	anti-CD27 antibody	NCT0146013
ADOPTIVE IMMUNOTHERAPY		
Autologous CAR.CD30 EBV specific-cytotoxic T-lymphocytes (relapsed)	EBV+ CD30+ HRS cells; CD30+ HRS cells	NCT01192464
DOWNSTREAM SIGNALING PATHWAYS		
MLN4924 (relapsed)	NFκB via inhibition of Ned8	NCT00722488
Everolimus (relapsed)	PI3K signaling, mTOR, TNFR signaling	
1) Everolimus and Panobinostat		1) NCT00918333
2) Everolimus and Lenalidomide		2) NCT01075321

[a]Includes patients with HL and NHL;

NR: not reported; NA: not available, ORR: overall response rate; CR: complete response; PR: partial response, PFS: progression free survival; TTP: time to progression; DOR: duration of response; ASCT: autologous stem cell transplant; BV: brentuximab vedotin; AVD: adriamycin, vinblastine, dacarbazine; ECAPP B: brentuximab vedotin in combination with etoposide, cyclophosphamide, adriamcyin, procarbazine, prednisone and brentuximab; ECADD B: etoposide, cyclophosphamide, adriamcyin, doxorubicin, dacarbazine and brentuximab; ABVD: adriamycin, bleomycin, vinblastine, and dacarbazine; BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone.