Targeted Therapy in Relapsed Classical Hodgkin Lymphoma

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Abstract
Although frontline treatment of advanced Hodgkin lymphoma (HL) produces high cure rates, disease either will not respond to or will relapse after initial therapy in approximately a quarter of patients. Many patients with disease relapse can be successfully salvaged with second-line chemotherapy followed by autologous stem cell transplantation (ASCT). Patients whose disease relapses after ASCT are rarely cured. A unique pathophysiologic feature of HL is that the malignant Reed-Sternberg (HRS) cell is rare and resides within a microenvironment of inflammatory and immune-related cells. The recent FDA approval of the anti-CD30 antibody-drug conjugate brentuximab vedotin (BV) for patients with either primary refractory HL or those whose disease relapses after ASCT represents a major advance in therapy. This article focuses on BV and other novel agents that target the HRS cell surface, intracellular signaling pathways, and tumor microenvironment. (JNCCN 2013;11:968-976)

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Classical Hodgkin lymphoma (HL) is one of the most curable cancers. Patients whose disease relapses and fails to respond to second-line therapy, including autologous hematopoietic stem cell transplant (ASCT), have an estimated median survival of less than 3 years because of limited therapeutic options. The hallmark of HL is the rare malignant Hodgkin Reed-Sternberg (HRS) cell, which develops in a microenvironment of non-neoplastic cells, including B cells, T cells, plasma cells, eosinophils, and mast cells and the cytokines they control and release. Thus, it is thought that the cross-talk between HRS cells, immune-mediated cells, and cytokines plays an important role in the pathogenesis of HL. Recent therapeutic strategies have focused on the development of agents that target 1) receptor molecules highly expressed on the HRS cell surface; 2) intracellular proteins governing the signaling pathways that regulate the survival and proliferation of HRS cells; and 3) reactive cells and cytokines in the tumor microenvironment (Figure 1). This article highlights some of the agents either approved or in development for relapsed/refractory (R/R) HL (Table 1).

**HRS Cell Surface Targets**
The most-developed targeted therapy in HL involves the CD30 receptor, which is a member of the tumor necrosis factor (TNF) receptor family involved in signaling pathways that regulate HRS cell proliferation. CD30 is expressed on most HRS cells, but is rarely seen on other cell types, making it an ideal target for therapy. Clinical studies using naked monoclonal antibodies targeting CD30 (MDX-030 and SGN-30) failed to demonstrate meaningful anti-tumor activity, largely attributed to poor antigen binding or neutralization of anti-CD30 by circulating soluble CD30. Attempts to improve antigen binding led to a phase I trial with a humanized anti-CD30 antibody, Xmab2513, and final results for safety and efficacy are awaited. In an attempt to increase cytotoxicity, the anti-CD30 chimeric antibody cAC10 was conjugated to a synthetic antimicrotubule agent, monomethyl auristatin E, producing the antibody–drug conjugate brentuximab vedotin (BV). Compared with naked antibodies, encouraging results were reported in 2 phase I studies of BV, with an overall response rate (ORR) of approximately 50% in heavily pretreated patients. Subsequently, a pivotal phase II trial of BV confirmed these results in patients whose disease had relapsed after ASCT, with an ORR of 75% (complete response, 34%). The median progression-free survival was 5.6 months and the median duration of response was 20.5 months. The therapy was well tolerated, and grade 3 or higher adverse events included neutropenia (20%), thrombocytopenia (8%), anemia (6%), and peripheral sensory neuropathy (8%).

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**Figure 1** Targeted inhibition of the Hodgkin Reed-Sternberg cell surface, the intracellular signaling pathway, and the tumor microenvironment. Abbreviations: DACI, histone deacetylase inhibitor; GPCR, G-protein-coupled receptor; HIF, hypoxia-inducible factor; HRS, Hodgkin Reed-Sternberg; IKK, IκB kinase; NF-κB, nuclear factor κB; RTK, receptor tyrosine kinase; VEGF, vascular endothelial growth factor.

agent was approved by the FDA in 2011 for patients with R/R HL for whom ASCT failed, for those who are not ASCT candidates, or after failure of at least 2 prior multiagent chemotherapy regimens. Emerging data suggest that retreatment with this agent results in an ORR of 57%. Ongoing studies are focusing on evaluating BV in combination with chemotherapy as front-line therapy of HL.

Other agents that target the HRS cell surface include those directed at receptors for CD40, TNF-related apoptosis-inducing ligand (TRAIL) and co-stimulatory molecules of the B7 family, such as CD80.
Activation of the CD40 receptor on HRS cells induces nuclear factor κB (NF-κB), cytokine, and chemokine secretion, promoting increased production of survival proteins. Of the 2 monoclonal antibodies targeting CD40, SGN-40 and HCD122 (lucatumumab), only HCD122 included patients with R/R HL, and in a phase II study, 3 of 18 patients experienced a partial response. Dose-limiting toxicities included clinically asymptomatic and reversible grade 3/4 elevation of amylase/lipase or transaminase enzymes.

TRAIL is a death protein expressed by activated T and natural killer (NK) cells. HL cell lines express TRAIL receptors R1, R2, and R4, which are thought to signal apoptosis. Agonistic anti–TRAIL-R1 and anti–TRAIL-R2 antibodies induced cell death in HL cell lines. However, a phase I trial of an agonistic anti–TRAIL-R2 antibody, AMG655, in combination with vorinostat or bortezomib, was suspended because of low patient accrual (ClinicalTrials.gov identifier: NCT00791011).

CD80 is a membrane-bound costimulatory molecule that regulates T-cell activity and is constitutively expressed by HRS cells. Galiximab is a primatized IgG1 monoclonal antibody, which binds to CD80 with high affinity and induces cell death via antibody-dependent cellular cytotoxicity (ADCC). Despite minimal toxicities, disappointing results were reported in a phase II trial in patients with R/R HL, with an ORR of only 6.9% and median time to progression (TTP) of 1.6 months.

CD25 is the alpha chain of the interleukin (IL)-2 receptor and is present on nearly all HRS cells. However, disappointing results were reported in a phase I trial of the anti-CD25 immunotoxin, RFT5-SPMT-dgA; major side effects related to vascular leak syndrome occurred and efficacy was limited, with only 2 of 15 patients experiencing a partial response.

HRS cells also express both IL-13 and IL-13 receptors. A phase I/II trial with a monoclonal antibody targeting IL-13, TNX-650, has been initiated in R/R HL, and no results have been reported to date (ClinicalTrials.gov identifier: NCT00441818).

Intracellular Survival Pathway Targets
Aberrant expression of pro-survival proteins can be targeted by small molecules that are either broad or selective pathway inhibitors. Broad inhibitors modulate histone deacetylase (HDAC) inhibitors, proteasome inhibitors, and heat shock protein 90 (HSP90) inhibitors. Selective inhibitors target the PI3K/Akt/mTOR pathway and the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway.

Epigenetic changes have been implicated in silencing B-cell genes in HRS, and are a proposed mechanism whereby HRS survive because of escape from immunosurveillance. Histone acetyltransferases and HDAC enzymes mediate posttranscriptional histone modification, and the balance between histone acetyltransferases and HDACs is crucial for gene expression and transcription of proteins involved in cell proliferation and survival. Based on their homology of accessory domains to yeast HDACs, the 18 currently known human HDACs are classified into 4 groups (I–IV). Class III is nicotinamide adenine dinucleotide (NAD)–dependent, and regulates chromatin structure. Classes I, II, and IV are zinc-dependent. Class I and IV HDACs are constitutively nuclear proteins involved in cell proliferation, whereas class II HDACs shuttle between the nucleus and the cytoplasm and are thought to regulate genes that promote cell growth. Vorinostat and panobinostat inhibit HDAC classes I and II and are considered pan-HDAC inhibitors, whereas MGCD0103 and entinostat preferentially inhibit class I HDACs (isotype-selective inhibitors). The HDAC targets that produce the maximum clinical benefit with the least side effects, particularly the benefit of broad HDAC class inhibition versus selective inhibition, are unknown.

Results of a phase II study of oral vorinostat in 25 patients with R/R HL were disappointing, with an ORR of only 4%. Promising results have been reported in a phase II trial of panobinostat, with 23% of patients experiencing a partial response and 4% of patients experiencing a complete response, with a median progression-free survival of 6.1 months. The main toxicities were grade 3 and 4 thrombocytopenia (79%), anemia (21%), and neutropenia (21%). Mocetinostat has been evaluated in a single-agent phase II trial in R/R HL. Dose levels of 85 to 110 mg were given orally 3 times per week. In the intent-to-treat analysis of efficacy, 8 of 23 (35%) patients treated with the 110-mg dose achieved a partial response or better; however, the drug was poorly tolerated.

The subsequent study was amended and clinical activity (21% partial response) was seen at a lower dose level of 85 mg with decreased toxicity.
The most frequent treatment-related adverse events of grade 3 or higher were myelosuppression, fatigue, and pneumonia. Four patients experienced serious adverse events, including pericardial effusion, 3 of which were grade 3 or higher. Cumulatively, these data suggest that HDAC inhibitors have activity in R/R HL, with a toxicity profile that differs from BV.

HRS cells consistently demonstrate constitutive transcription factor NF-κB activity. In vitro studies in HL cell lines treated with PS-341 (bortezomib), a known inhibitor of NF-κB, show strong antiproliferative activity. Despite the fact that 93% of patients were able to complete treatment without dose reductions, the CALGB phase II clinical trial evaluating bortezomib monotherapy in 30 patients with R/R HL failed to show a clinical response. This lack of antitumor activity of single-agent bortezomib in R/R HL was substantiated by subsequent studies.

Two clinical studies have evaluated bortezomib in combination with chemotherapy in R/R HL. A phase I trial of intravenous bortezomib on days 1 and 4 of standard ifosfamide, carboplatin, and etoposide (ICE) chemotherapy cycles enrolled 12 patients, with an ORR of 69%. The regimen caused greater myelosuppression than ICE alone, and transient transaminitis of grade 2 or lower; however, no dose-limiting toxicities occurred. Currently, a phase II study comparing ICE alone versus bortezomib plus ICE is ongoing (ClinicalTrials.gov identifier: NCT00967369). A second study treated 18 patients with 3-week cycles of bortezomib, 1 mg/m² on days 1, 4, 8, and 11, plus gemcitabine, 800 mg/m² on days 1 and 8. The ORR for all patients was only 22%, with significant grade 3 transaminase elevations; based on these results, this regimen was deemed to be less active and more toxic than other currently available treatments.

Heat shock proteins (HSPs) are cellular chaperone proteins that perform essential functions, such as protein folding, assembly, and transportation. They are overexpressed by HRS cells and are known to promote HRS cell survival via ERK, Akt, and NF-κB. Preclinical studies of HSP90 with the small molecule inhibitor geldanamycin derivative 17-AAG showed a time- and dose-dependent growth inhibition of HL cell lines. Furthermore, 17-AAG has been shown to be synergistic with doxorubicin. These observations have led to targeting HSP90 with 17-AAG in a phase II trial, and results are awaited (ClinicalTrials.gov identifier: NCT00117988).

In HL, constitutive activation of the PI3K/Akt/mTORC1 axis contributes to cell proliferation, survival, and angiogenesis. Everolimus, an mTOR inhibitor, has antiproliferative effects and leads to 80% growth inhibition of HL-derived cell lines. Clinical efficacy has been reported in a phase II trial of single-agent everolimus in R/R HL, with an ORR of 47% (8 partial responses and 1 complete response). The median TTP was 7.2 months. Four patients experienced grade 3 or higher pulmonary toxicity, but the drug was otherwise well tolerated and manageable with dose reductions. Results are considered promising for this heavily pretreated patient population. PI3Kδ inhibition is being evaluated in a phase II trial of GS-1101 (ClinicalTrials.gov identifier: NCT01393106). In vitro data also suggest that mTOR inhibitors may synergize with PI3K inhibitors and HDAC inhibitors in HL, and trials combining these agents are ongoing (ClinicalTrials.gov identifier: NCT00918333).

Aberrant activation of the JAK/STAT pathway also promotes proliferation and survival of HRS cells, and in vitro studies showed activity of JAK 2 inhibitors in HL. A recent phase I trial investigated the novel oral JAK2 inhibitor, SB1518, in patients with R/R HL. The minimum tolerated dose was not reached and treatment was well tolerated; however, no objective responses were seen in HL.

**Microenvironment Targets**

HL is an unusual malignancy in that the malignant HRS cells are a minor component of the tumor, the bulk of which is a mixed cellular infiltrate. The HRS cell furthers its own survival through evading immune regulation, and the interaction between HRS cells and immune and stromal cells is a hallmark of HL pathogenesis. The cross-talk between HRS cells and the reactive component is important in the survival and proliferation of HRS cells. The microenvironment seems to be vital to HRS cell survival, because cells do not survive readily in culture or immunodeficient mice (ClinicalTrials.gov identifier: NCT00441818). Increased galectin-1 and IL-10 concentrations secreted by HRS cells leads to decreased T-cytotoxic and Th1 responses, together with an increase of regulatory T (Treg) cells, which in turn suppresses both Th2 and PD1+ T-cell activity. Tumor-associated macrophages (TAMs) also
contribute to decreased T-cell activity through the STAT signaling pathway, and increased TAM levels are associated with shortened survival in patients with HL after conventional treatment or ASCT. Current treatment strategies have the goal of disrupting the microenvironment through selectively targeting its cellular components or T- and NK-cell activation to induce antitumor response. CD20 is rarely expressed on HRS cells; however, the microenvironment is a B-cell rich tumor. Data suggest that the B cells in the microenvironment deliver survival signals to HRS cells, including ligands for CD30 and CD40, and suppress the T-cell immune response via IL-10 production. Studies also show that circulating clonotypic B cells may be responsible for initiating HRS cells. In a pilot study of single-agent rituximab, patients received 6 weekly doses of rituximab, 375 mg/m². Five patients (22%) experienced a partial or complete response, and remissions were observed in patients with disease confined to the lymph nodes, irrespective of CD20 expression by HRS cells. Six of 7 patients with CD20⁺ HRS cells had resolution of their B symptoms after rituximab therapy, even in the absence of clinical response, suggesting that rituximab-depleted B cells were likely contributing to the cytokine-induced B symptoms.

Objective responses have also been reported in 16 of 33 patients (48%) with R/R HL treated with rituximab and gemcitabine, regardless of CD20 expression on HRS cells; however, the median failure-free survival was only 2.7 months. The regimen was generally well tolerated, with myelosuppression being the most common toxicity.

The latter results have led to the evaluation of rituximab in combination with ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) as a frontline treatment strategy. In a phase II study, 78 patients were treated with weekly rituximab for 6 weeks and standard ABVD for 6 cycles. At a median follow-up of 68 months, the 5-year event-free and overall survival rates were 83% and 96%, respectively, and were better than institutional historical data with ABVD alone. The most frequent treatment-related grade 3 or higher adverse events were neutropenia, fatigue, and nausea. Another phase II study of rituximab-ABVD for frontline treatment of HL reported 3-year event-free and overall survival rates of 83% and 98%, respectively. In this study, the persistence of detectable circulating clonotypic B cells was associated with a greater relapse frequency. In both studies, the addition of rituximab to ABVD did not increase toxicity, and additional studies are ongoing (ClinicalTrials.gov identifiers: NCT00654732 and NCT00515554).

Given the exquisite sensitivity of HL tissues to radiotherapy, anti-CD20 radioimmunoconjugates such as yttrium-90 ibritumomab tiuxetan have also been evaluated. It is hypothesized that anti-CD20 radioimmunotherapy can potentially deplete reactive CD20⁺ B cells that provide survival signals to HRS cells, target the rare CD20⁺ tumor cells, and indirectly deliver radiation to CD20⁺ HRS cells with crossfire radiation from ibritumomab tiuxetan bound to CD20⁺ B cells in the microenvironment. Case reports suggest some evidence of activity, but numbers are too small to make any definitive conclusions. Currently, an ongoing clinical trial is investigating a different radioimmunoconjugate, iodine-131 tositumomab, in patients with R/R HL (ClinicalTrials.gov identifier: NCT00484874).

Although CD20-targeted therapies selectively deplete cellular components of the microenvironment, immunomodulators, such as lenalidomide, have the goal of activating cytotoxic T and NK cells to directly attack HRS cells. Two studies have evaluated the safety and efficacy of lenalidomide in patients with R/R HL. A multicenter phase II study of 36 patients treated with lenalidomide, 25 mg/d on days 1 through 21 of a 28-day cycle reported an ORR of 19%. In another study of 15 patients, 2 experienced partial responses, 7 had stable disease, and median TTP was 3.2 months. Grade 3/4 neutropenia and thrombocytopenia were the most common toxicities in both studies. A third study of 12 patients achieved an ORR of 50% and reported only grade 1/2 cytopenias. Collectively, these studies show that lenalidomide has activity as a single agent in HL, particularly in heavily pretreated patient populations, and is now being investigated in combination with therapies directed against the HRS cell, including HDAC (ClinicalTrials.gov identifier: NCT01460940) and mTOR (NCT01076543 and NCT01075321) inhibitors, and with AVD (adriamycin, vinblastine, and dacarbazine; NCT01056679) and bendamustine (NCT01412307) chemotherapy.

CD52 is another target, which is highly expressed in surrounding reactive B cells, T cells, and monocytes, but not on HRS cells. Depleting CD52⁺ cells in the microenvironment may disrupt survival...
signals to HRS cells. Alemtuzumab is a humanized monoclonal antibody directed against CD52, resulting in cell lysis via ADCC. Unfortunately, a phase II study investigating the clinical efficacy of alemtuzumab in R/R HL was terminated because of slow accrual (ClinicalTrials.gov identifier: NCT0129753). Currently a phase II study is evaluating alemtuzumab in combination with dose-adjusted EPOCH (etoposide, doxorubicin, vincristine, prednisone, and cyclophosphamide) in patients with R/R HL (ClinicalTrials.gov identifier: NCT01030900).

PD-L1 is a molecule expressed on antigen-presenting cells that engages the PD-1 receptor on T cells and inhibits T-cell receptor signaling. An increase in the number of PD-1+ lymphocytes has been shown to be an independent negative prognostic predictor of overall survival.57 Given the T-cell–rich microenvironment of HL, PD-L1 is a novel therapeutic target. Antibodies to PD-1 and PD-L1 have been developed and are currently being investigated in clinical trials (ClinicalTrials.gov identifier: NCT01660776).

HRS cells selectively overexpress the immunoregulatory glycan-binding protein galectin-1 (Gal-1) through an AP1-dependent enhancer. Data implicate HRS-cell Gal-1 in the development and maintenance of an immunosuppressive Th2/Treg-skewed microenvironment in HL. In co-cultures of activated T cells and HL cell lines, RNA interference-mediated blockade or posttranscriptional gene silencing of HRS cell Gal-1 increased T-cell viability and restored the Th1/Th2 balance. These data suggest that Gal-1 represents another potential therapeutic target for restoring immune surveillance in HL.58

Conclusions

After more than 3 decades, several promising agents have been identified for the treatment of HL. The approval of BV is rapidly changing the standard of care for this disease. As more novel biomarkers and drugs are discovered, the challenge will be how to best combine agents or sequence therapy to produce the most effective and least toxic clinical results. Future trials will likely offer a targeted therapeutic approach and result in improved outcomes in patients with R/R HL.

References


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Posttest Questions

1. CD30 is expressed on most HRS cells, but is rarely seen on other cell types, making it an ideal target for therapy.
   a. True
   b. False

2. Broad pathway inhibitors that target aberrant expression of pro-survival proteins include all of the following except:
   a. HDAC inhibitors
   b. JAK/STAT pathway
   c. Heat shock protein (HSP90) inhibitors
   d. Proteosome inhibitors

3. The following are true of microenvironment targets:
   a. The microenvironment is vital to HRS cell survival
   b. A goal of current treatment strategies is disrupting the microenvironment through selectively targeting its cellular components
   c. B-cells deliver survival signals to HRS cells
   d. CD20-targeted therapies selectively deplete cellular components of the microenvironment
   e. All of the above