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REVIEW

Novel treatment strategies for patients with relapsed classical Hodgkin lymphoma

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ABSTRACT

The treatment of patients with relapsed and refractory Hodgkin lymphoma (HL), especially those who relapse after autologous stem cell transplantation, remains challenging. Patients with HL whose disease relapses after stem cell transplantation are rarely cured with current treatment modalities, and have a median survival of less than 3 years. Since no new drugs have been approved by the FDA for HL in more than three decades, there is a clear unmet medical need for drug development for this patient population. New treatment strategies that are based on targeting oncogenic signaling pathways are currently explored. This review will focus on emerging new treatment modalities that are currently under investigation for patients with relapsed classical HL.

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Hodgkin lymphoma (HL) is a rare human B-cell lymphoid cancer representing 11.4% of all lymphomas in the United States.[1] The treatment of HL has been evolved over the past three decades, and modern therapy is expected to successfully cure more than 80% of the patients. Despite this rather rare successful achievement in medical oncology, the current treatment continues to lack specificity and to induce unacceptable long-term toxicities that paradoxically shorten patients' survival. Furthermore, patients who are not cured with front-line or second-line therapy, including stem cell transplantation, have an estimated median survival of less than 3 years.[2] As the median age of this patient population is the mid-30s, the impact of early mortality on the number of years lost from productive life is more significant than many other cancers. However, because HL is a rare cancer that is highly curable, the development of new drugs for the treatment of HL has been very slow. Clearly, drug development in this area will address a significant unmet medical need.[3] With recent advances in our understanding of HL pathology, biology, and immunology, several therapeutic targets have been identified and are currently under preclinical and clinical investigation (Fig. 1).[3,4] The aim of drug development in HL is not only to further improve the cure rate, but also to decrease toxic effects of therapy. This review will focus on the most promising new drugs that are currently in clinical trials for the treatment of patients with relapsed classical HL.

1. Brentuximab vedotin (*SGN-35*)

The dense expression of CD30 by HRS cells coupled with its highly restricted expression makes it an obvious target for therapeutic monoclonal antibody.[5,6] Results from two clinical studies using first-generation naked anti-CD30 monoclonal antibodies in patients with relapsed HL have been disappointing, perhaps reflecting their poor antigen binding and/or effector cell activation properties (Table 1).[7,8] In an alternate strategy, the anti-CD30 antibody cAC10 was conjugated to a synthetic anti-microtubule agent, monomethyl auristatin E (MMAE), resulting in a novel immunotoxin conjugate brentuximab vedotin (SGN-35).[9] Brentuximab vedotin was recently evaluated in two phase I clinical trials in patients with relapsed HL and ALCL. In the first phase I study, brentuximab vedotin was administered every three weeks. Forty-five patients with relapsed HL and anaplastic large cell lymphoma (ALCL) were treated with escalating doses (0.1 to 3.6 mg/kg) by intravenous infusions every three weeks. The treatment was reasonably well tolerated, with neutropenia and hyperglycemia being dose-limiting toxicities. Neuropathy was also observed in some patients, especially after repeated dosing. Remarkably, 88% of the patients demonstrated tumor reductions, of whom 17 (37%) achieved partial or complete remissions.[10] In a second phase I study, 37 patients (31 with HL) were treated with brentuximab vedotin that was administered on a weekly schedule for 3 consecutive weeks in four-week cycles. Dose-limiting toxicities included grade 3 gastrointestinal toxicity and grade 4 hyperglycemia. The overall response rate was 46% (29% CRs). [11] Based on these encouraging results, a pivotal phase II trial recently completed enrollment of 104 patients treated using 1.8 mg/kg given every three weeks.

2. Panobinostat and other histone deacetylases (HDAC) inhibitors

Post-transcriptional histone modification plays an important role in regulating gene transcription and is mediated by several of enzymes, including histone acetyltransferases (HATs) and histone deacetylation (HDACs).[12] These enzymes mediate acetylation and deacetylation of

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Table 1
Summary of results of selected novel agents in relapsed Hodgkin's lymphoma (HL). HDACs indicates histone deacetylases; mTOR, mammalian target of rapamycin.

Agent	Target	Route	Phase	N	PR	CR	PR + CR	1st author
MDX060 [7]	CD30	IV	II	47	2	2	4 (8%)	Ansell
SGN30 [8]	CD30	IV	II	38	0	0	0 (0%)	Forrero-Torres
SGN35 [10]	CD30	IV	I	45	10	7	17 (37%)	Younes
SGN35 [11]	CD30	IV	I	31	6	10	16 (46%)	Fanale
Panobinostat [25]	HDACs	Oral	II	13	7	0	7 (58%)	Dickinson
Panobinostat [26]	HDACs	Oral	II	129	29	4	33 (26%)	Sureda
MGCD0103 [30]	HDACs	Oral	II	21	6	2	8 (38%)	Bociek
Vorinostat [31]	HDACs	Oral	II	25	1	0	1 (4%)	Kirshbaum
Everolimus [45]	mTOR	Oral	II	19	8	1	9 (47%)	Johnston
Lenalidomide [47]	?	Oral	II	35	5	1	6 (17%)	Fehniger
Lenalidomide [48]	?	Oral	II	15	2	0	2 (13%)	Kuruvilla

specific lysine amino acid residues on histone and non-histone proteins that regulate a variety of proteins that are involved in cell proliferation, survival, angiogenesis, and immunity.[13–15] To date, 18 HDACs have been identified in humans, and are grouped in two major categories: zinc-dependent HDACs and NAD-dependent HDACs.[16,17] Furthermore, HDACs are classified into four major classes: Class I (HDAC 1, 2, 3, 8, and 11); Class II (HDAC 4, 5, 6, 7, 9, and 10); Class III (SIRT 1–7), and Class IV (HDAC 11) (Fig. 2). Class III is NAD-dependent, whereas Classes I, II, and IV are zinc dependent. At the present time, several clinical grade pharmacologic inhibitors of the zinc-dependent HDACs are available for clinical trials, but only two inhibitors, vorinostat and romidepsin have been approved by the FDA for treating relapsed cutaneaus T-cell lymphoma. Vorinostat (SAHA) and panobinostat (LBH589) inhibit HDAC Classes I and II (pan-HDAC inhibitors). MGCD0103 and entinostat (SNDX-275, formerly MS-275) preferentially inhibit Class I HDACs (isotype-selective HDAC inhibitors).

There are several rationales for using HDAC inhibitors (HDACis) for the treatment of HL. For example, although HRS cells are of B-cell origin, they infrequently express B-cell antigens.[18] This loss of B-cell phenotype has been reported to be epigenetically regulated and may be therapeutically reversible.[19,20] Several HDAC inhibitors have antiproliferative activity in HL-derived cell lines in vitro. In a recent study, vorinostat was shown to induce cell cycle arrest and apoptosis in HL cell lines and to synergize with chemotherapy.[21] Similarly, the isotype-selective MGCD0103 has a potent anti-lymphoma activity by modulating the expression of a variety of survival proteins and provides mechanistic rationale for combining Class-I HDAC inhibitors with proteasome inhibitors and TRAIL.[22] In vitro experiments with entinostat (SNDX-275) demonstrated that this HDACi has a dual antiproliferative effect by downregulation of XIAP and induction of apoptosis, and possibly by modulation of the immune response.[23] Furthermore, vorinostat inhibited STAT6 phosphorylation and transcription in HL cell lines, an effect that was associated with a decrease in the expression and secretion of T_h2-type cytokines and chemokines, including thymus and activation-regulated chemokine (TARC/CCL17) and IL-5, and an increase in T_h1-type cytokines/chemokines, including a profound increase in IP-10 levels.[21] HDACis, alone or in combination with hypomethylating agents, have been shown to

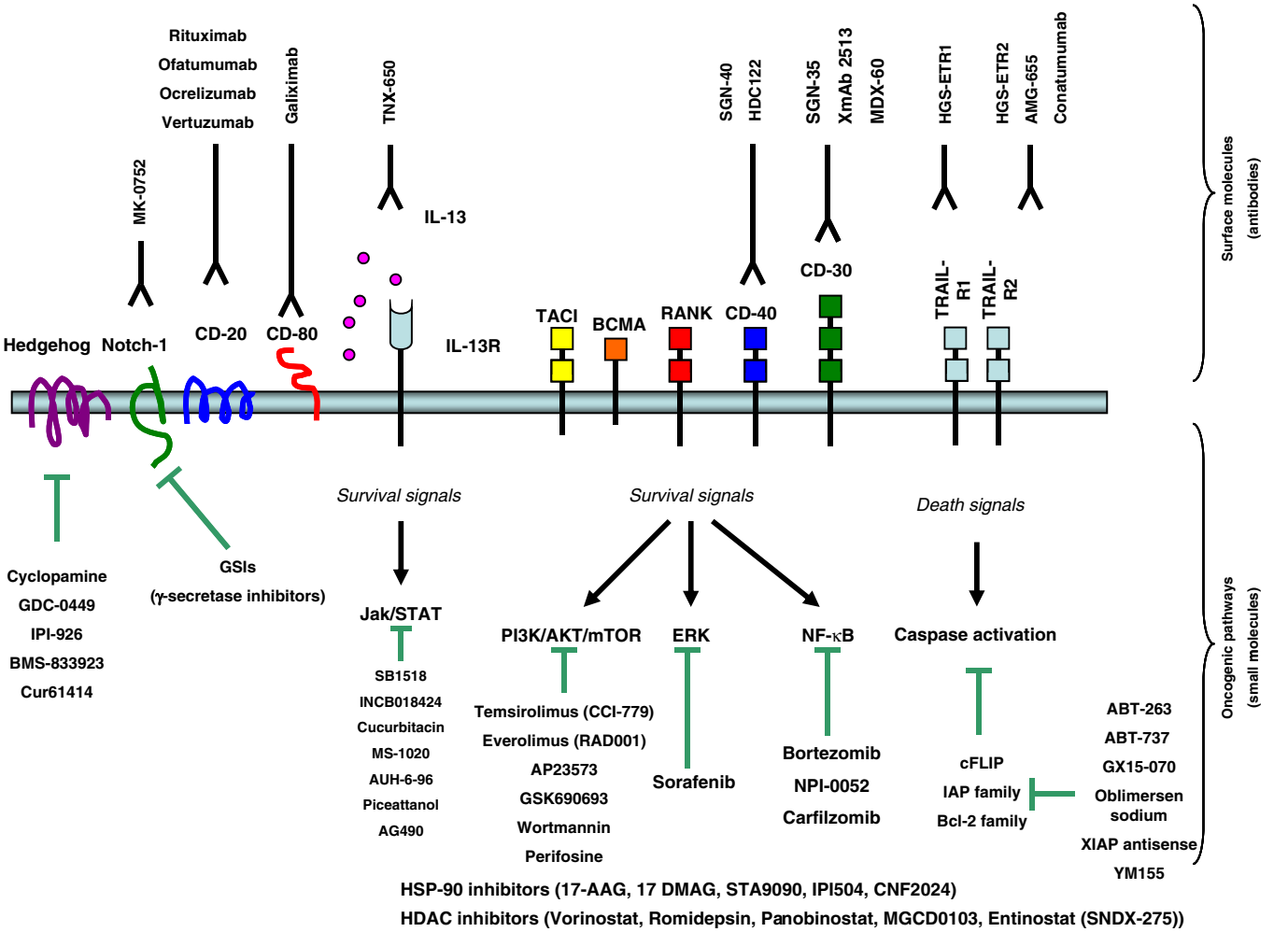

Fig. 1. Targeted therapy of HRS cells. HRS cells express a variety of receptors and antigens that can be targeted by monoclonal antibodies. Many of these receptors trigger well defined signaling pathways that promote HRS cell survival. These signaling pathways can be targeted by a variety of small molecules.

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