Hodgkin Lymphoma: Targeting the Tumor Microenvironment as a Therapeutic Strategy

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Abstract: Over the past decade, new biologic insights have revealed the key role of the tumor microenvironment in the pathogenesis of classical Hodgkin lymphoma (cHL). The primary Hodgkin Reed-Sternberg (HRS) tumor cells normally constitute less than 1% of the tumor cellularity in cHL, and are surrounded by an abundant and heterogeneous inflammatory infiltrate. The cross talk between the HRS cells and the cells of the cHL microenvironment sustains tumor growth and survival. An improved understanding of this phenomenon has led to the development of novel antitumor strategies that alter the cHL microenvironment, changing it from protective to cytotoxic. Developing new strategies remains a high priority because—despite the curability of cHL—as many as one-third of advanced-stage patients will relapse after first-line therapy. Furthermore, only half of relapsed patients will obtain long-term disease control through autologous stem cell transplant. In this review, we will provide an overview of the role of the cHL microenvironment in disease biology, the agents currently available or under investigation targeting the cHL microenvironment, and the most promising and innovative treatment platforms being evaluated in clinical trials.

Keywords
Checkpoint inhibitors, Hodgkin lymphoma, immune modulation, nivolumab, novel therapies, pembrolizumab, relapsed disease, tumor microenvironment

Introduction

Hodgkin lymphoma (HL), a B-cell neoplasm, constitutes 10% of all lymphomas, with more than 9000 estimated new cases every year and more than 1100 deaths a year in the United States.[1] Classical HL (cHL) accounts for 95% of cases. The second subtype, nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), is uncommon and has distinct clinicopathologic features and a different tumor cell immunophenotype. Thus, we will not discuss NLPHL in this review. Classical HL has a bimodal age-distribution curve, with age-specific incidence rates peaking in young adults and a second smaller peak in the elderly. As many as 90% of patients diagnosed with early-stage disease are cured with frontline therapy, whereas only 70% of

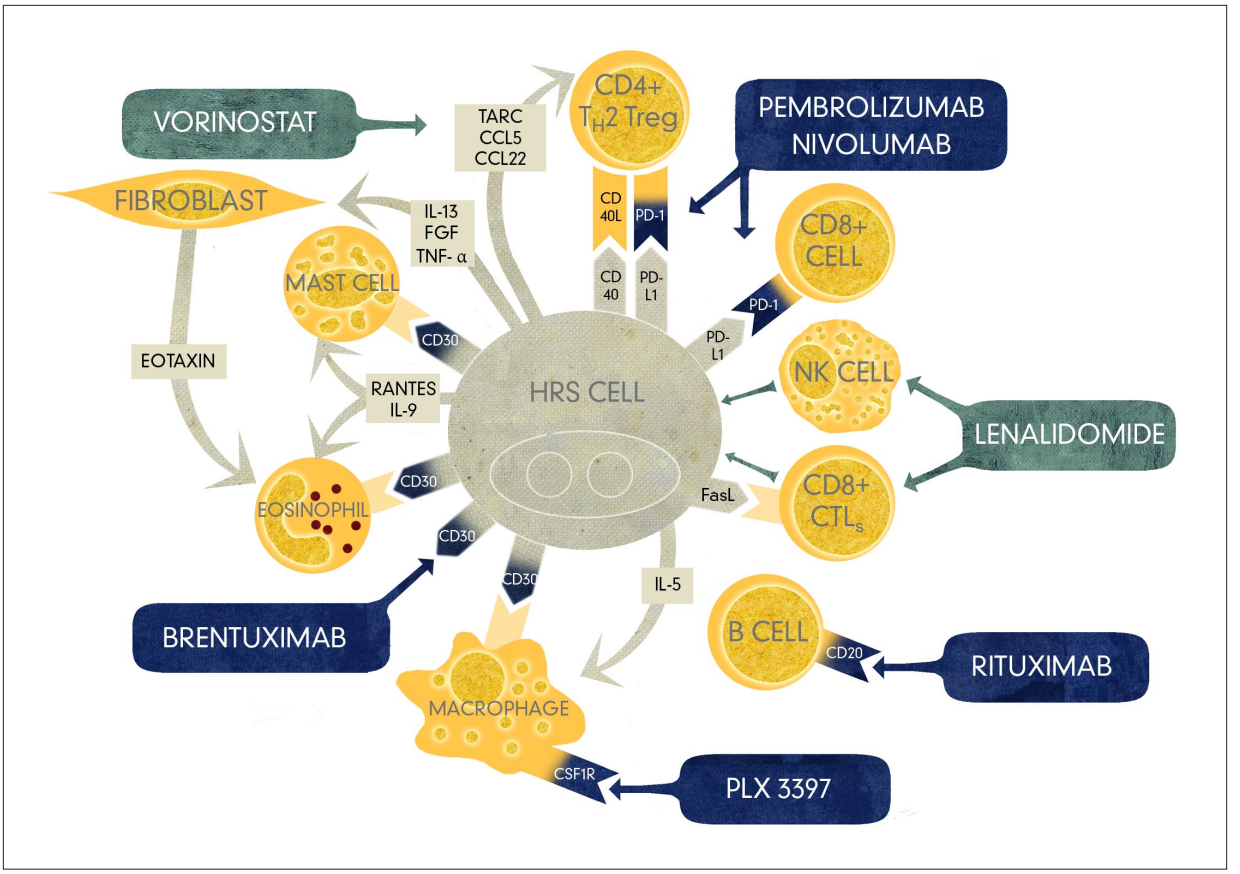

Figure. Selection of novel agents targeting the microenvironment. In blue: monoclonal antibodies targeting specific cell receptors. In green: agents that affect the microenvironment acting on cytokines and chemokines or activating immune cells. In gray: Hodgkin Reed-Sternberg cell. In yellow: immune system cells.

CCL, chemokine ligand; CSF1R, colony-stimulating factor 1 receptor; CTLs, cytotoxic T cells; FasL, Fas ligand; FGF, fibroblast growth factor; HRS, Hodgkin Reed-Sternberg; IL, interleukin; NK, natural killer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; RANTES, regulated on activation normal T cell expressed and secreted; TARC, thymus and activation–related chemokine; Th2, T helper 2; TNF-α, tumor necrosis factor α; Treg, T regulatory.

patients with advanced-stage cHL are cured.[2] For relapsed patients or patients refractory to frontline therapy, salvage chemotherapy and autologous stem cell transplantation (ASCT) are curative in only 50% of patients.[3] Prognosis remains poor for patients with refractory disease who are unable to achieve disease control prior to ASCT and for patients relapsing after ASCT, for whom no further curative options are available currently.

The biology of cHL demonstrates the key role of the tumor microenvironment in promoting and sustaining lymphomagenesis. Classical HL has a distinctive cellular composition, consisting of a minority of Hodgkin Reed-Sternberg (HRS) tumor cells (0.1%-1.0%) surrounded by an abundant inflammatory infiltrate consisting of B cells, T cells, natural killer (NK) cells, mast cells, eosinophils, histiocytes/macrophages, and neutrophils.[3] The cross talk between the HRS cells and the cells of the tumor microenvironment supports cHL growth and survival. Whether the HRS cells drive and sustain their microenvironment, or the inflammatory microenvironment itself stimulates the development of the HRS cells is unknown. Examples of this cross talk between HRS cells and the microenvironment include the following cytokines and chemokines: (1) regulated on activation, normal T-cell expressed and secreted (RANTES); (2) thymus and activation–related chemokine (TARC); (3) chemokine ligand 20 (CCL20); and (4) CCL22. These recruit an abundant CD4-positive T-cell population that predominantly expresses a T helper 2 (Th2) and T regulatory (Treg) phenotype.[4,5] In contrast to Th1 cells, which promote cell-mediated immune responses, Th2 cells promote activation of B cells and immunoglobulin production. Treg cells suppress the activation of other immune cells, in particular CD8-positive cytotoxic T lymphocytes (CTLs).[6] This imbalance in the Th1:Th2 ratio in the tumor microenvironment supports HRS cell survival and provides protection from immunosurveillance. In parallel, HRS cells also directly induce apoptosis in CD8-positive CTLs through overexpression of the Fas ligand.[7]

Table 1. Results of Selected Clinical Trials With Novel Microenvironment Agents as Monotherapy in Heavily Pretreated Patients With Relapsed or Refractory cHL

Drug Agent	Phase	Number of Patients	% of Patients After ASCT	Response Rate	Status of the Study	Duration of Response
Nivolumab[20]	1	23	78%	ORR, 87% CR, 17%	Ongoing (CheckMate 039, NCT01592370)	NA
Pembrolizumab[21]	1b	29	69%	ORR, 66% CR, 21% (1-y SD, 20%)	Ongoing (KEYNOTE-013, NCT01953692)	NA
Lenalidomide[25]	2	36	86%	ORR, 19%	Completed	NA
Rituximab[34]	2	22	81%	ORR, 22%	Completed	EFS, 7.8 mo
PLX3397[42]	2	20	NA	ORR, 5%	Completed	PFS, 56 d
Panobinostat[48]	2	129	78%	ORR, 27% CR, 4%	Completed	TTR, 2.3 mo

ASCT, autologous stem cell transplantation; CR, complete response; d, days; EFS, event-free survival; mo, months; NA, not available; ORR, overall response rate; PFS, progression-free survival; SD, stable disease; TTR, time to recurrence; y, year.

Table 2. Selection of Ongoing Clinical Trials Evaluating Novel Agent Combinations as Frontline Therapy and for Relapsed or Refractory Disease in Patients With cHL

Treatment	Phase	Disease Status	Clinical Trial	Status[49]
Ipilimumab and brentuximab vedotin	1	RR	NCT01896999	Recruiting
Lenalidomide and temsirolimus (Torisel, Wyeth)	1/2	RR	NCT01076543	Recruiting
Lenalidomide and bendamustine (Treanda, Teva)	1/2	RR	NCT01412307	Recruiting
Lenalidomide and romidepsin (Istodax, Celgene)	1/2	RR	NCT01742793	Recruiting
Lenalidomide and panobinostat	2	RR	NCT01460940	Recruiting
R-ABVD vs ABVD	2	Advanced stage, first line	NCT00654732	Ongoing, accrual completed
R-ABVD vs ABVD-RT	3	Early stage, first line	NCT00992030	Ongoing, accrual completed
Rituximab and brentuximab vedotin	Pilot	RR	NCT01900496	Recruiting

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ABVD-RT, doxorubicin, bleomycin, vinblastine, dacarbazine, radiation therapy; CR, complete response; EFS, event-free survival; ORR, overall response rate; PFS, progression-free survival; R-ABVD, rituximab, doxorubicin, bleomycin, vinblastine, dacarbazine; RR, relapsed or refractory; SD, stable disease; TTR, time to recurrence.

Mast cells, eosinophils, and macrophages are attracted by cytokines such as RANTES, interleukin 5 (IL-5), and IL-9, and directly stimulate HRS cell proliferation through interactions between the CD30 ligand and CD30.[8] Fibroblasts, recruited by IL-13, fibroblast growth factor, and tumor necrosis factor alfa (TNF-α), are responsible for fibrosis in the tumor tissue and the production of cytokines and chemokines such as eotaxin and RANTES. These cytokines and chemokines participate in the further recruitment of eosinophils and Tregs in the microenvironment.[9]

This biology provides a strong rationale for investigating therapeutic approaches that target the tumor microenvironment in cHL as a stand-alone strategy and in conjunction with HRS cell targeting. A summary of these different approaches is outlined in the figure. This review provides an overview of therapeutic strategies targeting the microenvironment of cHL, including checkpoint inhibitors, immunomodulatory drugs (IMiDs), drugs targeting peritumoral CD20-positive B cells (rituximab [Rituxan, Genentech/Biogen Idec]), tumor-associated macrophages (TAMs), and histone deacetylase inhibitors (HDACIs) (Table 1). An overview of the ongoing clinical trials evaluating potential synergistic strategies of microenvironment-HRS targeting is also provided (Table 2).

Immune Activation Drugs: Checkpoint Inhibitors

One key mechanism of immune evasion demonstrated across a variety of solid tumors—and more recently, hematological malignancies—is the direct inhibition of CD8-positive CTLs by the activation of immune checkpoint pathways. The programmed cell death 1 (PD-1) receptor, a member of the B7 receptor family, functions as an important checkpoint in the downregulation of immune responses in normal hosts, contributing to tolerance to self-antigens.[10] The ligands for PD-1, programmed cell death ligand 1 (PD-L1) and PD-L2, are upregulated in conditions of chronic

inflammation, such as during viral infection (eg, HIV,[11] hepatitis B virus [HBV],[12] and hepatitis C virus [HCV][13]), in asthma,[14] and in the tumor microenvironment of both solid tumors and lymphomas.[15] Blockade of the PD-1/PD-L1 interaction has shown promising activity in multiple solid tumors, prompting the approval of 2 PD-1 inhibitors. Nivolumab (Opdivo, Bristol-Myers Squibb), a fully human immunoglobulin G4 (IgG4) anti–PD-1 antibody that blocks the interaction between PD-1 and PD-L1/PD-L2, is approved for unresectable or metastatic melanoma, for disease progression following treatment with ipilimumab (Yervoy, Bristol-Myers Squibb) and a BRAF inhibitor, and for metastatic squamous non–small cell lung cancer with progression on or after platinum-based chemotherapy. Pembrolizumab (Keytruda, Merck), a humanized IgG4 monoclonal antibody with a high affinity for PD-1 that blocks the binding of PD-L1 and PD-L2, is approved for unresectable or metastatic melanoma and for disease progression following ipilimumab and a BRAF inhibitor.

Histopathologic studies have demonstrated that PD-1 is highly expressed on the peritumoral lymphocytes in the tumor microenvironment of cHL. Correspondingly, HRS cells express PD-L1,[16] suggesting that the PD-1/PD-L1 interaction between the HRS cells and the peritumoral lymphocytes may induce exhaustion in peritumoral lymphocytes, which contributes to immune dysfunction and tumor tolerance in the microenvironment. The genes encoding PD-L1/PD-L2 are located on chromosome 9p24.1 and are commonly amplified in nodular sclerosing cHL, the most common histologic subtype of cHL, suggesting that this mechanism of immune escape might be of particular relevance in this lymphoma.[17] Epstein-Barr virus (EBV) infection, which is found in nearly half of cHL patients, may further drive the expression of PD-L1 on HRS cells in EBV-positive patients cells.[18]

Clinical data from recently presented early-phase trials confirmed the activity of checkpoint inhibition for heavily pretreated patients with cHL. Results from the phase 1 trial CheckMate 039 (NCT01592370) were presented at the 2014 annual meeting of the American Society of Hematology (ASH).[19] In this study, 23 patients with relapsed or refractory cHL received 3 mg/kg of nivolumab at week 1, week 4, and then every 2 weeks until disease progression or complete response (CR) or for a maximum of 2 years. The primary endpoint was safety; the secondary endpoint was overall response rate (ORR). Approximately one-third of the patients had received more than 6 prior regimens, 78% had undergone a prior transplantation, and 78% had received prior brentuximab vedotin (Adcetris, Seattle Genetics). Adverse events of any grade occurred in 96% of the patients, but only 22% were grade 3 and none were grade 4. Pneumonitis and colitis were the most common drug-related adverse events, and 1 case of pancreatitis was observed. Overall, nivolumab had a safety profile similar to that observed with solid tumors. The ORR for nivolumab was 87%, including a 17% CR rate; 3 additional patients had stable disease (SD). The progression-free survival (PFS) rate at 23 weeks was 86%, and the median duration of response is still being evaluated. Analyses of pretreatment tumor specimens from 10 patients revealed copy-number gains in and increased expression of PD-L1 and PD-L2 in all 10 patients.[20] These data supported the breakthrough therapy designation for nivolumab, granted in May 2014 by the US Food and Drug Administration for the treatment of patients with cHL after failure of ASCT and brentuximab vedotin. CheckMate 205 (NCT02181738), a registrational trial evaluating nivolumab in patients with cHL after failure of ASCT, is currently ongoing and recruiting participants.

Pembrolizumab has been investigated in a cohort of cHL patients included in the KEYNOTE-013 trial (NCT01953692), and results from the cHL patient subgroup were presented at the 2014 annual ASH meeting.[21] This ongoing multicenter open-label phase 1b clinical trial enrolled patients with a variety of relapsed or refractory hematologic malignancies who were heavily pretreated, including 31 patients with relapsed or refractory cHL. Pembrolizumab was administered at a dose of 10 mg/kg every 2 weeks for 24 months until disease progression or intolerable toxicity. Responses were assessed at week 12, and every 8 weeks thereafter. The primary endpoint was CR rate, with secondary endpoints including ORR, PFS, and safety. In this study, 31 patients with relapsed cHL were enrolled at the time of data presentation, with results available for 29 patients. Patients had a median age of 32 years (range, 20-67 years); 52% had received 5 or more lines of therapy, 69% had failed ASCT, and 28% were ineligible for ASCT. Bulky lymphadenopathy was present in 31% of patients. With a median follow-up of 153 days (range, 1-341 days), 9 patients discontinued treatment for disease progression (n=7), adverse effects (n=1), or CR (n=1). Among the 29 patients enrolled in the study, 20 patients (69%) were still receiving therapy. The median duration of response had not been reached at the time of data presentation. The treatment was well tolerated with few extramedullary side effects, most commonly grade 1 or 2 thyroid disorders and pneumonitis, each observed in 10% of the patients. There were no deaths or grade 4 adverse events. The ORR was 66%, including a CR rate of 21% and a partial response (PR) rate of 45%; the SD rate was 21%. Notably, among the patients with SD, a few have been receiving treatment for nearly 1 year, suggesting the possibility of prolonged stabilization of disease growth. A phase 2 trial of pembrolizumab in cHL is planned for the first half of 2015 (KEYNOTE-087). Using IMiDs in combination with checkpoint inhibitors could be extremely promising; however, the reported data have been from

phase 1 trials and remain preliminary. Larger confirmatory studies, which are ongoing, have the potential to redefine treatment paradigms in all aspects of cHL management.

Another promising strategy derived from cHL biology is combining checkpoint inhibitors with HRS-targeting drugs. The rationale is to enhance the tumor-directed immune activation of the tumor microenvironment and simultaneously target tumor bulk, providing antigen release with a targeted therapy that can further stimulate immunity. A phase 1 study is currently ongoing and enrolling patients that explores the combination of the anti-CD30 antibody-drug conjugate brentuximab vedotin with the anti-cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) antibody ipilimumab, a human IgG1κ monoclonal antibody specific for human CTLA-4 that increases the population of activated T effector cells and blocks the negative regulation of regulatory T cells[22] (NCT01896999). This study plans to add subsequent arms evaluating the combinations of brentuximab vedotin with nivolumab and with nivolumab plus ipilimumab.

Immunomodulatory Therapies

IMiDs are a group of compounds that are structurally and functionally related to thalidomide (Thalomid, Celgene). Their biological effects include inhibition of angiogenesis by decreasing vascular endothelial growth factor (VEGF) secretion by stromal cells, inhibition of proinflammatory cytokines (ie, IL-6 and TNF-α), stimulation of cellular immunity, and the ability to directly induce growth arrest and apoptosis of tumor cells. Lenalidomide (Revlimid, Celgene) is an IMiD that has been extensively used in multiple myeloma,[23] is approved for myelodysplastic syndrome harboring a 5q-chromosomal abnormality,[24] and has shown activity in cHL[25] and in several B-cell malignancies.[26,27]

Lenalidomide inhibits angiogenesis by decreasing VEGF secretion by stromal cells and inhibits the secretion of proinflammatory cytokines, such as IL-6 and TNF-α. This drug has a direct effect on the innate and adaptive immune system, acting as a potent costimulator for T-cell activation by increasing production of T-cell cytokines and activating CD8-positive CTLs and NK cells. Strikingly, lenalidomide enhances antibody-dependent cellular toxicity (ADCC) and mononuclear cell activity, leading to tumor cell apoptosis.[28]

In a multicenter phase 2 study, 36 patients with heavily pretreated relapsed or refractory cHL (87% post-ASCT and 55% with refractory disease) were treated with lenalidomide at 25 mg daily on days 1 through 21 of a 28-day cycle until disease progression or excessive toxicity. The ORR was 19%, with 1 patient achieving a CR and 6 patients achieving a PR. The treatment was well tolerated, with moderate hematologic toxicity.[25] Other smaller studies confirmed the activity and favorable toxicity profile of lenalidomide as single-agent treatment in heavily pretreated relapsed cHL, which makes it an appealing drug to use in combination with chemotherapy or other novel agents.[29,30] Several trials investigating lenalidomide combinations with chemotherapy, mammalian target of rapamycin (mTOR) inhibitors, and HDACI are currently ongoing (Table 2). Additionally, an ongoing trial is evaluating the role of lenalidomide as maintenance therapy after ASCT (NCT01207921).

Monoclonal Antibodies Targeting Peritumoral B Cells: Rituximab

Primary HRS cells rarely express CD20; in contrast, the tumor microenvironment contains an abundant infiltrate of CD20-positive B cells. The scientific rationale for targeting these CD20-positive B cells is somewhat controversial. Some data suggest that a B cell–rich tumor microenvironment is associated with favorable outcome[31,32]; however, data also show that CD20-positive B cells in the microenvironment deliver survival signals to HRS cells, including ligands for CD30 and CD40, and suppress T cell–mediated immune responses by producing IL-10.[33]

Based on this hypothesis, a pilot study was conducted in 2003 using rituximab, a monoclonal anti-CD20 antibody, to target peritumoral CD20-positive B cells in patients with relapsed or refractory cHL. Patients were treated with 6 weekly doses of rituximab at 375 mg/m^2. Objective tumor response was determined 3 weeks after completion of the last dose of rituximab and every 3 months thereafter. The ORR was 22% in 22 patients, and the median duration of response was 7.8 months. Remissions were observed irrespectively of CD20 expression by the primary HRS tumor cells, which express CD20 infrequently.[34]

Two subsequent phase 2 trials have evaluated the activity of rituximab plus ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) in newly diagnosed advanced-stage cHL patients. In the first trial, 78 patients were treated with rituximab weekly for 6 weeks followed by standard ABVD for 6 cycles. At 68 months, the event-free survival (EFS) and overall survival (OS) rates were 83% and 96%, respectively. The combination was well tolerated overall, with neutropenia, fatigue, and nausea being the most common grade 3 or 4 adverse events.[35] In a second trial of 49 patients with stage 2 to 4 untreated cHL, comparable results were reported; the 3-year EFS and OS were 83% and 98%, respectively.[36] Two additional clinical trials evaluating the benefit of adding rituximab to front-line therapy have completed accrual, but the results have not yet been reported (NCT00654732, NCT00992030).

To date, the addition of rituximab to other chemotherapy regimens has not shown significant activity. The combination of rituximab with gemcitabine in relapsed or refractory cHL in a prospective clinical trial showed an ORR of 48%, which appeared to be independent of HRS

cell CD20 expression; however, the duration of response was very short (2.7 months).[37] The combination of rituximab with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) escalated (NCT00515554) was presented at the 2014 ASH meeting. In this study, 440 patients with early interim (ie, after 2 cycles of BEACOPP escalated) positron emission tomography (PET)–positive advanced-stage cHL were randomly assigned either to 4 additional cycles of BEACOPP escalated or to BEACOPP escalated and rituximab. With a median follow-up of 35 months, Kaplan-Meier PFS estimates were largely overlapping (log-rank *P*=.99), with an estimated 3-year PFS of 91.4% for BEACOPP (95% CI, 87.0%-95.7%) and 93% for R-BEACOPP (95% CI, 89.4%-96.6%). Accordingly, OS was not different (96.5% vs 94.4% at 3 years, respectively; *P*=.31).[38] Rituximab is also being evaluated in combination with brentuximab vedotin as first-line salvage therapy in a currently ongoing pilot study (NCT01900496). No interim data analysis is available at this time.

Targeting Tumor-Associated Macrophages: PLX3397

Macrophages are represented in the microenvironment compartment across all types of neoplasms. The presence of abundant macrophages in the tumor microenvironment has been linked to poor prognosis in several cancers, including solid tumors and hematologic malignancies.[39] TAMs produce a variety of growth factors, cytokines, and chemokines that promote tumor growth, angiogenesis, invasion, and/or metastasis.[40]

Increased numbers of CD68- and CD163-expressing TAMs have been associated with inferior survival in patients with newly diagnosed cHL, patients treated with standard chemotherapy, and patients who received ASCT.[41] Steidl and colleagues used gene expression profiling in tumor samples from 130 newly diagnosed cHL patients and found a cellular signature of peritumoral macrophages that was associated with poor prognosis. This finding was validated using CD68 expression in immunohistochemistry to detect TAM infiltration in an independent cohort of 166 patients. Interestingly, increased numbers of CD68-positive cells were significantly associated with reduced PFS after ABVD chemotherapy independent of other recognized adverse clinical and laboratory parameters.[32]

These studies provided the rationale for evaluating the multitargeted tyrosine kinase inhibitor PLX3397 in cHL. PLX3397 binds to and inhibits the phosphorylation of stem cell factor receptor (KIT), colony-stimulating factor 1 receptor (CSF1R), and FMS-like tyrosine kinase 3 (FLT3), resulting in the inhibition of tumor cell proliferation and down-modulation of macrophages, osteoclasts, and mast cells. Unfortunately, the results of a phase 2 single-agent clinical trial in 20 patients with relapsed or refractory cHL treated with PLX3397 demonstrated only modest activity (ORR, 5%) and a median PFS of 56 days, despite successful inhibition of both CSF1R and KIT.[42] More studies are needed to further clarify the role of CSF1R in cHL and to better elucidate whether combination strategies that target this axis have a therapeutic role.

Epigenetic Therapies: Histone Deacetylase Inhibitors

Epigenetic effects have been implicated in silencing several B-cell genes in HRS cells, and this mechanism has been proposed to promote HRS cell proliferation and survival.[43] HDACIs are a novel class of anticancer compounds that alter gene expression and regulate differentiation, cell cycle progression, and apoptosis of malignant cells. HDACIs use multiple epigenetic mechanisms, including chromatin condensation and histone acetylation.[44,45] Additionally, HDACIs impact the tumor microenvironment. Vorinostat (Zolinza, Merck) is immunomodulatory, inhibiting signal transducer and activator of transcription 6 (STAT6)–mediated Th2 cytokine and chemokine secretion in the microenvironment and thereby creating an unfavorable milieu for tumor growth. Treatment of cHL with an HDACI decreased the secretion of the inhibitory cytokine TARC in vitro.[46]

The therapeutic role of HDACIs has been investigated in cHL, including the drugs vorinostat,[46] mocetinostat,[47] and panobinostat (Farydak, Novartis),[48] with panobinostat demonstrating the highest activity as a monotherapy. A cohort of 129 patients with heavily pretreated relapsed or refractory cHL (median age, 32 years) and a median of 4 prior therapies was treated with panobinostat at 40 mg orally 3 times a week. This group had an ORR of 27%, including a 23% PR rate and a 4% CR rate. The median PFS was 6.1 months, with an estimated 1-year OS of 78%. The primary toxicity was severe (grade 3 or 4) thrombocytopenia in 79% of the patients. Responses were associated with early reductions in serum TARC levels.[48] Unfortunately, owing to the high incidence of hematologic toxicity, development of this agent in cHL is not currently ongoing.

Conclusion

Recent insights in the pathogenesis of cHL have highlighted the crucial role of the inflammatory infiltrate in this disease, in which the malignant cells uniquely constitute only a tiny minority of the total cellularity. As our understanding of the complicated cross talk between the microenvironment and the HRS cell deepens, an increased number of potential targets for therapeutic interventions are being identified. An improved understanding of the

complex interaction of HRS cells and inflammatory cells will hopefully lead to new treatment paradigms based on observations in cHL biology that will travel from bench to beside. These approaches and the concurrent development of predictive biomarkers to tailor therapeutic approaches to patients with the relevant biology will hopefully allow us to achieve the future goals of limiting toxicity from chemotherapy for low-risk patients and improving the cure rate for all cHL patients.

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