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Tackling PD1i resistance in Hodgkin lymphoma

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In this issue of *Blood*, Mei and colleagues report the results of a trial in which the histone deacetylase inhibitor vorinostat was combined with the programmed cell death protein-1 inhibitor (PD1i) pembrolizumab, demonstrating an impressive response rate, including in patients who were refractory to prior PD1i therapy.¹

Classic Hodgkin lymphoma (cHL) is highly sensitive to treatment with inhibitors of PD1i, thought to be at least partly due to high expression of PD-L1, the ligand for PD1, by the malignant Hodgkin and Reed-Sternberg (HRS) cell. The genetic locus for *PD-L1* is found on chromosome 9p24, which is itself subject to frequent copy number alterations.² Initial phase 2 trials demonstrated high and durable response rates of single-agent nivolumab and pembrolizumab in relapsed or refractory cHL.^{3,4} Although some response are durable, most patients either fail to respond or lose their response at some point during therapy.

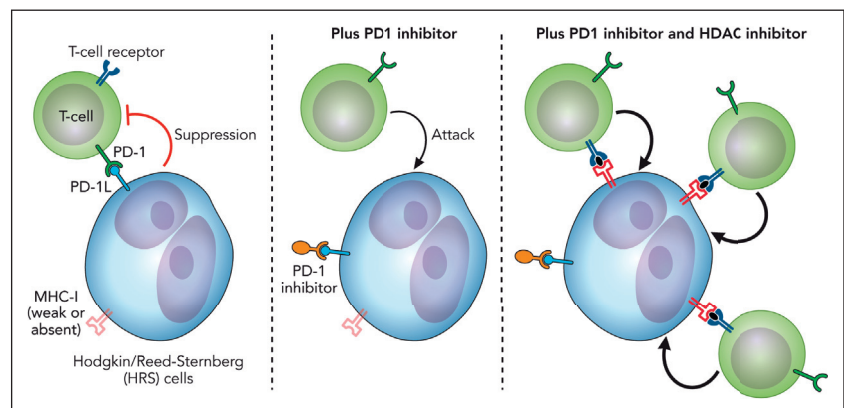
It was by no means obvious that PD1 inhibition would work in cHL as HRS cells frequently do not express both major histocompatibility complex (MHC) class I and β -2-microglobulin. This would make a CD8⁺ cytotoxic T-cell-mediated mechanism of action unlikely. Further work has instead focused on CD4⁺ T cells as these are often colocalized with HRS cells and PD-L1 expressing tumor-associated macrophages.⁵ Moreover, in a subset of patients who had relapsed more than 12 months after an autologous stem cell transplant, expression of MHC class II (the receptor for CD4) was associated with a longer progression-free survival.² It is hypothesized that CD4⁺ effector T cells maybe at least one of the mediators of efficacy of PD1i in cHL. Further support comes from analysis of immune signatures in patients with cHL on PD inhibitor therapy. An expansion of CD4 (but not CD8) T-cell receptor clonal diversity was associated with response, most strikingly seen in those achieving a complete response.⁶

HDAC inhibitors also have demonstrable, albeit modest, activity in relapsed or refractory cHL with a large phase 2 study of panobinostat reporting a rather disappointing overall response rate of 27% and complete response rate of 4%.⁷ Significant interest in HDAC inhibitors in combination with immunotherapy agents like PD1i has arisen with reports of an immunostimulatory action. Epigenetic modifying agents have been shown in various models to enhance MHC class I expression, increase antigen presentation, and increase T-cell infiltration to the tumor microenvironment.⁸

It can therefore be hypothesized that HDAC inhibition may lead to an improved or even restored sensitivity to PD1 inhibition in cHL. In this study reported by Mei and coworkers, 32 patients with relapsed or refractory disease were treated with vorinostat and pembrolizumab, 30 at the recommended phase 2 dose. Of note, almost

all had received prior brentuximab vedotin therapy and 78% had received prior PD1i therapy with 56% being PD1i refractory. The best overall response rate was 72% with 56% of PD1i refractory patients responding and 11% having a complete metabolic response. The investigators secured pretreatment and postprogression biopsies in 3 patients. Although there was no relative difference in immune cell subsets, there was an increased density of CD4⁺ and CD8⁺ T cells in 2 out of 3 patients. In an attempt to investigate the potential mechanisms leading to immune cell expansion, Hodgkin lymphoma cell lines were treated with vorinostat and subjected to RNA sequencing. Upregulated genes included groups of genes involved in cytotoxic T-cell recruitment, T-cell costimulation, and antigen presentation. Although Hodgkin cell lines are not necessarily a true reflection of cHL in vivo, this lends support to a model such as that illustrated in the figure whereby HDAC inhibitors may sensitize some patients to PD1 inhibition. Such sensitization (or indeed resensitization) may include increased expression of immune receptors by HRS cells, increased recruitment, and enhanced activity of cytotoxic T cells.

Mei and colleagues have made an important contribution, showing proof of principle that PD1i activity may be enhanced by incorporating a rational, nonchemotherapy, targeted agent in combination. Although it is increasingly appreciated that PD1i combined with cytotoxic chemotherapy can lead to very high response rates, a desirable outcome in the field is to move away from cytotoxic agents and introduce targeted therapies



A model showing how the addition of an HDAC inhibitor may enhance the activity of a PD1i in cHL through increased immune receptor expression (such as MHC class I), increased recruitment, and activation of T cells. Professional illustration by Patrick Lane, ScEYence Studios.

predicted to synergize with PD1is. To this end a number of trials of drugs targeting multiple immune checkpoints are ongoing, including combined LAG3 and PD1 inhibition and combined TIM3 and PD1 blockade. Hodgkin lymphoma was one of the first cancers to be frequently cured by radiotherapy and then by combination chemotherapy. It will be fascinating to see if immunotherapy combinations hold similar potential.

Conflict-of-interest disclosure: G.P.C. reports research funding received from Bristol Myers Squibb. ■

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<https://doi.org/10.1182/blood.2023021283>

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THROMBOSIS AND HEMOSTASIS

Comment on [Brocklebank et al](#), page 1371

Narrowing the knowledge gap in atypical HUS

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In this issue of *Blood*, Brocklebank et al¹ present the largest single-center cohort with suspected complement-associated atypical hemolytic uremic syndrome (CaHUS) treated with eculizumab. CaHUS is a rare kidney disease in which complement activation occurs on endothelial cell surfaces, causing a thrombotic microangiopathy. The authors provide detailed information of the clinical characteristics at presentation and a complete genetic analysis of these patients from the National Renal Complement Therapeutics Centre (NRCTC) in the United Kingdom.

Patients with CaHUS typically present with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. Approximately half of individuals have an inherited (complement factor H, complement factor B, and C3 mutations) or acquired (factor H autoantibodies [FHAs]) complement abnormality identified. Treatment historically included supportive

care with/without plasma exchange, but outcomes were poor, with end-stage kidney disease (ESKD) or death occurring at first presentation in many patients. More recently, small, single-arm trials of eculizumab in CaHUS have been reported; however, the rarity of the disease has made clinical trials difficult. In the United Kingdom, all cases of suspected CaHUS are referred to the

NRCTC, and these cases are the subject of this report.

The authors report a significantly higher 5-year ESKD-free survival in eculizumab-treated patients with CaHUS (85.5%) compared with an untreated, genotyped matched cohort (39.5%). While recognizing the limitations of this type of comparison, these data support the efficacy of eculizumab in CaHUS. The study also reports a low relapse rate, which has been reported by other researchers, and clearly argues against the need for lifelong use of this expensive drug.^{2,3}

It is important to examine the differences between the eculizumab-treated cohort and the control group. The latter was selected on the basis of the presence of a pathogenic complement genetic variant or FHAs, thus supporting a diagnosis of CaHUS. Clinical information at presentation for the control group was not available. The eculizumab-treated group consisted of patients referred to the NRCTC, with a suspected diagnosis of CaHUS. Pathogenic variants or FHAs were detected in only 47% of patients, raising the question of the presence of complement dysregulation in the other 53%.

Although the study provides useful data on the epidemiologic features of CaHUS, its presentation, clinical course, and outcome, and delineates novel causes of "secondary" HUS/thrombotic microangiopathy (TMA), it is evident that much remains to be understood about this rare disease.

The most important outstanding issues raised by this study include the following:

1. The difficulty of diagnosing CaHUS. The treated cohort included 51 patients who were later diagnosed as having secondary thrombotic microangiopathy (positive predictive value, 192/243 = 79%). Conversely, 544 patients were referred for eculizumab therapy, but not treated, when a diagnosis of CaHUS was considered unlikely. After full evaluation, a pathogenic mutation was found in 40 of these patients. Thus, the diagnostic accuracy is limited at best, even in an esteemed center of expertise: with a sensitivity of 69% and a specificity of 90%. Clearly, biomarkers are needed to make an early and accurate diagnosis, and ascertain that patients receive the