Review Article

Hodgkin lymphoma and PD-1 blockade: an unfinished story

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Abstract: Classical Hodgkin lymphoma (cHL) is characterized genetically by near-universal alterations in 9p24.1, which result in constitutively increased expression of programmed cell death 1 (PD-1) receptor ligands on malignant Reed-Sternberg (RS) cells and evasion of immune destruction. Based on this genetic susceptibility, anti-PD-1 monoclonal antibodies have been tested in patients with relapsed or refractory (R/R) cHL and have shown impressive response rates and durable remissions, leading to the accelerated approval of two PD-1 inhibitors in this setting, nivolumab and pembrolizumab. These drugs have changed the clinical trial landscape for cHL. PD-1 blockade is now being tested in virtually every phase of treatment with the goal of capitalizing on its benefit earlier in a patient's treatment course. In addition, based on its tolerability and single agent activity, PD-1 inhibitors are being paired with many other agents including chemotherapy and immunotherapy. Early experience combining PD-1 inhibitors with ipilimumab or brentuximab suggests that this strategy is feasible, but longer-term follow-up is necessary to determine the true benefit of these combinations. Given the numerous possible combination partners, a better understanding of the mechanisms of primary and acquired resistance will be important to rationally design trials of drug combinations that include PD-1 inhibitors. Finally, early clinical data suggests that treatment with PD-1 blockade in conjunction with allogeneic hematopoietic stem cell transplant (HSCT) (either prior to transplantation or for relapse after transplantation) may be associated with an increased risk of immunologic complications, but also the potential for a synergistic anti-cancer effect. Ongoing investigation is necessary to guide treatment strategies to minimize toxicity and maximize efficacy in this setting. While initial trials of PD-1 inhibitors in cHL were met with much excitement, additional investigation is necessary to determine how anti-PD-1 therapy will be optimally incorporated into the treatment paradigm for patients with cHL.

Keywords: Hodgkin lymphoma; programmed cell death 1 (PD-1) receptor ; PD-L1; PD-L2; immunotherapy; nivolumab; pembrolizumab

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Introduction

The programmed cell death 1 (PD-1) receptor is an inhibitory immune checkpoint that is expressed on T cells and other hematopoietic cells. Upon T cell activation, expression of PD-1 is increased. Once engaged by one of its ligands (PD-L1 or PD-L2), PD-1 recruits SH2 domain-containing phosphatases, leading to T cell inactivation (1). Many tumors have co-opted elements of the PD-1 pathway in an attempt to inactivate tumor-specific T cells to evade immune detection and destruction (1). A growing understanding of this and related mechanisms of tumor immune evasion, together with the development of multiple monoclonal antibodies inhibiting the PD-1 pathway, has resulted in an explosion of clinical trials across many tumor types in recent years. These trials have fundamentally

changed the treatment of multiple cancers, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, and others (2-4).

Classical Hodgkin lymphoma (cHL) is characterized by an unusual tumor environment comprised of rare malignant Reed-Sternberg (RS) cells surrounded by much more numerous immune cells, which are unable to mount an anti-tumor immune response. RS cells maintain this microenvironment by secreting chemokines (CCL5, CCL17, CCL22) which recruit and support a T cell population that is disproportionately composed of Th2 cells and T regulatory cells (5). In addition, RS cells almost uniformly express PD-L1 and PD-L2 which upon binding to PD-1 on tumor-infiltrating lymphocytes can shift tumor-specific T cells to an exhausted phenotype (6). Constitutive expression of PD-1 ligands is driven by very frequent genetic alterations at 9p24.1, which contains genes for both PD-L1 and PD-L2. The locus also includes genes for JAK2 and additional transducers and activators of the JAK2/STAT pathway, which drive further expression of PD-1 ligands (7). Furthermore, EBV infection, which occurs in a sizable minority of cHL patients (5), can itself result in increased PD-1 ligand expression through a separate mechanism (8). In a retrospective analysis of 108 patients with cHL, 99% of patients at diagnosis had a detectable alteration in 9p24.1 including 56% of patients with copy gain and 36% of patients with amplification. A higher level of alteration in 9p24.1 was associated with increased expression of PD-1 ligands as well as inferior PFS with frontline treatment (9).

Clinical trials of PD-1 inhibitors in cHL

Based on compelling preclinical data demonstrating the high frequency of 9p24.1 alterations and the likely importance of the PD-1 pathway in the pathobiology of this tumor, patients with cHL were included as independent cohort expansions on phase I clinical trials of nivolumab and pembrolizumab (*Table 1*). In both studies, patients were heavily pretreated with the majority having progressed after both brentuximab vedotin (BV) and autologous hematopoietic stem cell transplant (HSCT). The 23 patients enrolled on CHECKMATE-039, the phase I trial of nivolumab, achieved an investigator-assessed overall response rate (ORR) of 87%, including a complete response (CR) rate of 17%. Responses were durable with 35% of patients responding at 1.5 years and a median progression-free survival (PFS) not reached after 101 weeks at the time of last report. All 10 patients with available tissue samples for analysis had copy number alteration in 9p24.1 and increased expression of both PD-L1 and PD-L2 on RS cells (10). KEYNOTE-013, the phase I study of pembrolizumab, reported similar investigator-assessed overall (65%) and CR rates (16%) for 31 cHL participants, with a median PFS of 11.4 months (11). Responses were again durable with a median duration of response (DOR) not yet reached after a median of 24.9 months of follow-up (15). Again, tissue samples from participants showed almost universal expression of PD-L1 (94%) and PD-L2 (90%) on RS cells (11).

These results prompted the initiation of several phase II trials (*Table 1*). A Japanese phase II trial of 17 patients reported a centrally assessed ORR of 81% with a 25% CR rate (13). The phase II CHECKMATE 205 trial evaluated nivolumab in 243 patients with relapse after autologous HSCT and showed a high response rate regardless of BV treatment history. Among 63 BV-naïve patients in cohort A, the centrally assessed ORR was 65% with a CR rate of 29%, which was similar to cohorts B (ORR 68%, CR 13%) and C (ORR 73%, CR 12%), which enrolled patients with prior BV exposure before or after autologous HSCT. The median PFS for the three cohorts ranged from 12 to 18 months with a median DOR of 15 to 20 months (12,16). The phase II KEYNOTE-087 trial evaluated pembrolizumab in a similar population of patients with relapsed cHL after autologous HSCT, but also included a group of patients who were ineligible for autologous HSCT due to chemo-resistant disease. Among the entire cohort of 210 patients, the centrally assessed ORR was 69% and the CR rate was 22% (14). Notably, the response rates were similar for patients with higher-risk disease including 81 patients who were ineligible for autologous HSCT because of chemo-resistance (ORR 64%, CR 25%) (14) and the overlapping subgroup of 73 patients with primary refractory disease (ORR 80%, CR 23%) (17). Patients who had not achieved a response to BV also appeared to have similar benefit from pembrolizumab with an ORR of 72% (14).

In the two larger phase II studies, analysis of tissue biopsies showed frequent expression of PD-1 ligands on tumor cells. In addition, all 45 patients with evaluable tumor samples in CHECKMATE 205 had alterations in 9p24.1, including 26 patients with copy gain and 12 patients with amplification (12). Whereas alterations in 9p24.1 were previously linked to inferior outcomes to induction chemotherapy (9), 9p24.1 alterations and increased PD-L1 expression were associated with more favorable response to PD-1 blockade in both phase II studies (12,14). For

Table 1 Phase I and II trials of PD-1 inhibitors for relapse/refractory Hodgkin lymphoma

	CHECKMATE-039 (10)	KEYNOTE-013 (11)	CHECKMATE-205 (Cohort B) (12)*	Maruyama *et al.* (13)	KEYNOTE-087 (14)		
					Cohort 1	Cohort 2	Cohort 3
PD-1 inhibitor	Nivolumab	Pembrolizumab	Nivolumab	Nivolumab	Pembrolizumab	Pembrolizumab	Pembrolizumab
Phase	1b	1b	2	2	2	2	2
Patients (n)	23	31	80	17	69	81	60
Prior autologous HSCT	78%	71%	100%	29%	100%	0%	100%
Prior brentuximab	78%	100%	100%	100%	100%	100%	42%
Rate AEs resulting in treatment discontinuation	9%	6%	6%	18%		4%	
ORR	87%	65%	68%	81%	74%	64%	70%
CR	17%	16%	9%	25%	22%	25%	20%
PR	70%	48%	58%	56%	52%	40%	50%
PFS at 6 months	86%	66%	77%	60%		72.4%	
Median PFS	Not reached	11.4 months	14.8 months	Not reported		Not reached	
OS	Not reported	100% (at 6 months); 87% (at 12 months)	98.7% (at 6 months); 94.9% (at 12 months)	100% (at 6 months)		99.5% (at 6 months); 97.5% (at 9 months)	

*, Full results of CHECKMATE-205 for cohort A and C have not been published. HSCT, hematopoietic stem cell transplant; AE, adverse event; ORR, overall response rate; CR, complete response; PR, partial response; PFS, progression free survival; OS, overall survival.

example, all patients who achieved a CR to nivolumab in CHECKMATE 205 had PD-L1 expression in the 3rd or 4th highest quartiles, while all patients with progressive disease had PD-L1 expression in the lowest quartile (12). Despite the frequent expression of PD-1 and its ligands on immune cells within the tumor microenvironment, PD-L1 expression on intratumoral histiocytes and macrophages did not predict response to pembrolizumab (14).

These phase II trials led the U.S. Food and Drug Administration to grant accelerated approval for both nivolumab and pembrolizumab for R/R cHL. Confirmatory, randomized phase III studies for both drugs are ongoing with slightly different strategies. Pembrolizumab is being directly compared with BV (NCT02684292), a CD-30 directed antibody-drug conjugate that is itself associated with high ORR (61%) and CR rates (38%) for patients with relapsed cHL after autologous HSCT (18). In contrast, nivolumab is being given in combination with BV and compared against BV monotherapy in its confirmatory phase III trial (NCT03138499) (see "Combination therapy" below). However, the potential clinical impact of these trials may be clouded by the rapid evolution of treatment in this disease. First, in the near future, it is possible that few patients with R/R cHL will be BV-naive, which will make the comparison between BV and PD-1 blockade less relevant. In addition, establishing the superiority of pembrolizumab or BV + nivolumab over BV alone does not prove their superiority over what would be the practical clinical alternative, i.e., BV followed by PD-1 blockade upon progression.

The above trials conclusively showed that PD-1 blockade is an effective strategy in cHL. There are several additional checkpoint inhibitors that target the PD-1 pathway at the ligand level (PD-L1) rather than at the receptor level (avelumab, atezolizumab, durvalumab). Those agents are in earlier stages of clinical development in cHL (NCT02603419, NCT03120676, NCT02733042). In several solid tumors, treatment with PD-1 and PD-L1 inhibitors has had similar efficacy and safety (19-22). The situation is different in cHL, since both PD-L1 and PD-L2 are regularly and highly expressed on RS cells (7). The potential role of PD-L2 in enhancing immune evasion may favor receptor-level blockade; conversely, anti-PD-L1 antibodies may derive additional anti-tumor activity from direct binding to tumor cells and engagement of antibody-dependent cell-mediated cytotoxicity (ADCC), which would favor ligand-level blockade. Several ongoing phase I studies of these PD-L1 inhibitors include patients with cHL, which may provide preliminary answers regarding the relative efficacy of the two approaches.

Safety

The safety profile for nivolumab and pembrolizumab in patients with cHL is similar to that seen in other malignancies (23). In published trials of PD-1 blockade for cHL, the most common adverse events were diarrhea (27%), fever (23%), fatigue (21%), infusion reactions (21%), nausea (15%), pruritus (14%), rash (14%), and hypothyroidism (11%) (weighted average of published cHL studies) (10-14). Notably, pneumonitis, which is a rare but potentially fatal complication of PD-1 blockade, was seen at similar rates (any grade 3.9%, grade 3 or higher 0.8%) in published trials in cHL (10-14), compared to prior trials in solid tumors (any grade 2.7%, grade 3 or higher 0.8%) (24), despite prior treatment with multiple potentially pneumotaxic medications (bleomycin, carmustine, etc.) in many patients. In the larger phase II trials, only a small minority of patients had AEs requiring treatment discontinuation (4–6%) (12,14). As PD-1 inhibitors are being used in earlier clinical settings and in combination with other drugs, vigilance regarding new or accentuated toxicities will be necessary, as is the case for example with PD-1 blockade administered in the context of allogeneic HSCT (see "Allogeneic HSCT" below).

Combination therapy with PD-1 blockade

Given the tolerability and efficacy of PD-1 blockade, many investigators have sought to utilize PD-1 inhibitors in combination with other drugs to improve response rates and to treat patients who have progressed on PD-1 therapy alone (*Table 2*). This approach has proven useful in metastatic melanoma were the combination of nivolumab and ipilimumab improves PFS in a least a subset of patients (25). CHECKMATE 039 tested a similar strategy by combining nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) in 65 patients with advanced hematologic malignancies. Among the 31 patients with cHL, the ORR (74%) and CR rate (19%) were similar to those seen for PD-1 monotherapy. After a median follow-up of 11.4 months, the median DOR, PFS, and OS had not been reached. However, combination therapy was associated with grade 3 or higher adverse events in 29% of patients (26). These early results suggest that combination therapy may be more toxic, without a clear increase in efficacy at least so far. However, longer-term follow-up is necessary to assess whether DOR or PFS

Table 2 Ongoing clinical trials of pembrolizumab and nivolumab in classical Hodgkin lymphoma

PD-1 inhibitor	NCT number	Phase	Therapy	Clinical setting
First-line therapy				
Nivolumab	NCT02181738 (Cohort D)	Phase 2	N+AVD	First-line therapy for cHL
Nivolumab	NCT03004833	Phase 2	N+AVD followed by 30 Gy involved-field radiation	First-line therapy for early stage unfavorable cHL
Nivolumab	NCT03033914	Phase 1	N+AVD	First line treatment for high-risk advanced stage cHL or older patients
Nivolumab	NCT01716806	Phase 2	Nivolumab and brentuximab vedotin	First-line therapy for cHL in older patients or patients who are ineligible or declined first-line chemotherapy
Nivolumab	NCT02758717	Phase 2	Nivolumab and brentuximab vedotin	First-line therapy for cHL in older patients or patients who are ineligible or declined first-line chemotherapy
Relapsed/refractory				
Pembrolizumab	NCT02684292	Phase 3	Pembrolizumab versus brentuximab vedotin	R/R cHL
Nivolumab	NCT03138499	Phase 3	Nivolumab plus brentuximab vedotin versus brentuximab vedotin alone	R/R cHL
Nivolumab	NCT03057795	Phase 2	Nivolumab and brentuximab vedotin	R/R cHL
Nivolumab	NCT02572167	Phase 1/2	Nivolumab and brentuximab vedotin	R/R cHL
Nivolumab	NCT02927769	Phase 2	Nivolumab and brentuximab vedotin	R/R cHL (patients aged 5–30)
Nivolumab	NCT03016871	Phase 2	NICE	R/R cHL prior to autologous HSCT
Pembrolizumab	NCT03077828	Phase 2	Pembrolizumab, ICE	R/R cHL prior to autologous HSCT
Nivolumab	NCT03015896	Phase 1/2	Nivolumab and lenalidomide	R/R cHL and NHL
Pembrolizumab	NCT02875067	Phase 1/2	Pembrolizumab and lenalidomide	R/R cHL and NHL
Nivolumab	NCT02940301	Phase 2	Nivolumab and ibrutinib	R/R cHL
Pembrolizumab	NCT02950220	Phase 1/1b	Pembrolizumab and ibrutinib	R/R cHL and NLH
Pembrolizumab	NCT02362035	Phase 1b/2	Pembrolizumab and acalabrutinib	R/R hematologic malignancies, including cHL
Pembrolizumab	NCT03150329	Phase 1	Pembrolizumab and vorinostat	R/R cHL and NHL
Nivolumab	NCT01896999	Phase 1	Combinations of nivolumab, brentuximab vedotin, and ipilimumab	R/R cHL
Nivolumab	NCT 01592370	Phase 1	Nivolumab plus ipilimumab or lirilumab	R/R hematologic malignancies, including cHL
Nivolumab	NCT02061761	Phase 1/2a	Nivolumab and BMS-986016 (anti-LAG-3)	R/R hematologic malignancies, including cHL
Pembrolizumab	NCT03179917	Phase 2	Pembrolizumab and involved-site radiation therapy	R/R cHL
Pembrolizumab	NCT02665650	Phase 1b	Pembrolizumab and AFM13 (bispecific anti-CD16/CD30 antibody)	R/R cHL
Nivolumab	NCT02973113	Phase 1	Nivolumab and EBV-specific T cells	R/R EBV positive lymphoma, including cHL

Table 2 (*continued*)

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PD-1 inhibitor	NCT number	Phase	Therapy	Clinical setting
Post-autologous HSCT				
Pembrolizumab	NCT02362997	Phase 2	Pembrolizumab	Maintenance therapy following autologous HSCT (cHL, DLBCL, T cell lymphomas)
Post-allogeneic HSCT				
Nivolumab	NCT01822509	Phase 1/1b	Nivolumab or ipilimumab	Relapse of a hematologic malignancy (including cHL) after allogeneic HSCT
Pembrolizumab	NCT02981914	Phase 1	Pembrolizumab	Relapse of a hematologic malignancy (including cHL) after allogeneic HSCT

N+AVD, nivolumab, adriamycin, vinblastine, and dacarbazine; NICE, nivolumab, ifosfamide, carboplatin, and etoposide; HSCT, hematopoietic stem cell transplant; cHL, classical Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

may be lengthened by the addition of ipilimumab. Several ongoing trials are investigating other combinations of immune checkpoint inhibitors including nivolumab plus BMS-986016 (an anti-LAG3 mAb) (NCT02061761) and nivolumab + lirilumab (an anti-KIR mAb) (NCT01592370). In addition, both nivolumab and pembrolizumab are being studied in conjunction with immunomodulatory drugs like lenalidomide and ibrutinib (NCT03015896, NCT02875067, NCT02940301, NCT02950220).

BV is another attractive combination partner for PD-1 inhibitors given its significant efficacy in R/R cHL and largely non-overlapping toxicity profile (18). Several ongoing trials are exploring this combination in various stages of treatment. In one ongoing study, 18 evaluable patients with R/R cHL and any number of prior treatments had an ORR of 89%, including 50% of patients who achieved a CR. However, there were two cases of pneumonitis, including one grade 5 event (27). A separate trial is using the same combination of nivolumab and BV for cHL patients with primary refractory disease or with relapsed disease after induction chemotherapy. At interim analysis, the overall and CR rates for the 59 evaluable patients were 85% and 63%, respectively. Grade 3 and higher AEs occurred in 33% of patients and 7% of patients required steroids for immune-related AEs (grade 4 pneumonitis/colitis, grade 2 pneumonitis, grade 3 colitis, and grade 3 AST elevation). At last report, 29 patients had received autologous HSCT (28). The apparently higher CR rates with this combination are encouraging; however, other salvage regimens have also demonstrated high CR rates (70–74%) (29-31), and longer follow-up is necessary to determine if a CR with a PD-1 based regimen, like a CR with conventional chemotherapy, is also a surrogate for post-autologous HSCT outcomes. Given the signal for increased efficacy for this combination, a randomized phase III trial is ongoing comparing nivolumab plus BV to BV alone in patients with R/R cHL (NCT03138499).

Numerous other combination strategies are in earlier stages of clinical testing. Hypomethylating agents (HA) may induce transcription of latent endogenous retroviral genes, facilitating presentation of neoantigens resulting in increased T cell recognition and destruction. In one small retrospective study, a higher CR rate was seen in cHL patients who had previously received a HA (5/5 patients) compared to patients with no prior HA treatment (2/4 patients) (32). Future studies combining PD-1 blockade and azacitidine are planned. For newly diagnosed patients, nivolumab is being studied in combination with the pared down induction chemotherapy regimen of adriamycin, vinblastine, and dacarbazine (AVD) or in combination with BV for older patients (NCT03004833, NCT01716806, NCT02758717). Nivolumab and pembrolizumab are both being studied with the salvage chemotherapy regimen of ifosfamide, carboplatin, and etoposide (ICE) in two additional clinical trials (NCT03016871, NCT03077828). Other strategies use PD-1 inhibitors to augment T cell or NK cell-based therapies. One trial adds nivolumab to treatment with EBV-specific T cells for cHL patient with EBV-positive tumors (NCT02973113). Another ongoing trial combines pembrolizumab with the novel CD16/CD30 bispecific antibody construct AFM13, which is designed to engage natural killer cells to target RS cells (NCT02665650). While these strategies may not all be successful, it is likely that some will result in increased response rates or improved DOR while maintaining a favorable toxicity profile.

Autologous HSCT

Most clinical trials have examined anti-PD-1 treatment for patients with relapsed disease after a prior autologous HSCT. However, maintenance or consolidative treatment with PD-1 blockade immediately following autologous HSCT may be an attractive strategy for several reasons. The potential therapeutic value of post-autologous consolidation in cHL was already shown with BV (33). Immediately following autologous HSCT, most patients have a minimal disease burden. In addition, high-dose chemotherapy results in increased antigen presentation, stimulation of the innate immune system, and a relative increase in CD8+ T cells and NK cells—all of which may augment the activity of PD-1 inhibition (34,35). A study of consolidation therapy with pidilizumab for patients with diffuse large B cell lymphoma undergoing autologous HSCT established the feasibility of this approach and showed encouraging efficacy data; however, uncertainty regarding the true target of pidilizumab halted subsequent development in cHL. Currently, pembrolizumab is being studied as consolidative therapy following autologous HSCT for patients with either cHL or non-Hodgkin lymphoma (NHL) (NCT02362997).

Allogeneic HSCT

Most patients with cHL can be cured with either conventional chemotherapy or autologous HSCT; however, approximately half of patients will relapse after autologous HSCT (36), and many will become candidates for allogeneic HSCT, which is the only therapy with known curative potential in this context. With the approval of two PD-1 inhibitors for R/R cHL, virtually all cHL patients undergoing allogeneic transplantation will have received a PD-1 inhibitor prior to allogeneic HSCT. However, the immunomodulatory effects of prior PD-1 blockade may alter the safety and efficacy of allogeneic HSCT. For instance, increased T cell activation mediated by blockade of the PD-1 pathway could enhance the graft-versus-tumor (GVT) effect resulting in low relapse rates, but could also exacerbate GVHD and other immune complications of HSCT. One multicenter, retrospective series reported the outcomes of 39 patients with lymphoma who underwent allogeneic HSCT after prior PD-1 blockade (37). Among the 31 patients with cHL, the 1-year cumulative incidence of relapse was lower than historical series; however, significant early toxicity was observed including a higher than expected rate of early severe acute GVHD and 4 early deaths from acute GVHD (3 patients) and hepatic sinusoidal obstruction syndrome (1 patient). In addition, 18% of patients developed a non-infectious febrile syndrome, which required prolonged courses of steroids. In this small study, transplantation with a bone marrow graft appeared to be associated with a lower rate of acute GVHD compared to a peripheral blood graft (0% *vs.* 32%, P=0.036), but other differences in transplant strategy (matched versus unmatched donor, conditioning regimen, GVHD prophylaxis regimen, time from last dose of PD-1 to HSCT) did not appear to affect the rate of GVHD, febrile syndrome, relapse, or survival. Exploratory biomarker analysis suggested that patients treated with PD-1 inhibitors prior to allogeneic HSCT had lower frequencies of circulating PD-1+ T cells compared to matched controls. These patients also had decreased ratios of T-regulatory cells to conventional CD4 and CD8 T cells, which has been associated with early GVHD in other studies (37).

Currently, the optimal transplant strategy for this population remains unclear, but would ideally incorporate strategies to reduce the risk of early GVHD and VOD. Some have proposed the use of post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis, which has been a very effective strategy to reduce GVHD in other high-risk populations (38-41). A single-center, retrospective analysis reported outcomes for 11 patients who had received a checkpoint inhibitor (6 nivolumab, 3 in combination with ipilimumab) prior to an allogeneic HSCT with PTCy-based GVHD prophylaxis (42). Despite dual checkpoint blockade in 3 patients and mismatched allografts in 6 patients (1 partially mismatched, 5 haplo-identical), rates of GVHD were low. Four patients developed grade II acute GVHD, all of whom responded to treatment (42). Additional investigation to identify a favorable transplant strategy is planned, but, in the meantime, allogeneic HSCT should be performed cautiously in these patients and could incorporate strategies to reduce early toxicity.

Although allogeneic HSCT is curative for a subset of patients with cHL, relapse remains unfortunately common (43-45). Following relapse, treatment options include additional chemotherapy, BV, donor lymphocyte infusion, and a second allogeneic HSCT; however, the toxicity of these regimens is significant and responses tend to be transitory. Preclinical studies suggest that alterations in signaling across the PD-1 synapse may play an important role in immune evasion and post-HSCT relapse (46-48). For example, in one mouse model there was differential

killing activity of donor cytotoxic T lymphocytes in different tissues that predicted anatomic location of relapse and could be explained at least in part by different levels of PD-L1 expression in host tissues. Importantly, anti-PD-1 treatment could restore cytotoxic T-lymphocyte activity in these tumor escape niches (49). On the other hand, anti-PD-1 therapy resulted in high rates of acute (50,51) and chronic (52) GVHD in other preclinical models.

Based on these preclinical studies, the efficacy and tolerability of PD-1 inhibitors in the pre-transplant setting, and the absence of effective alternatives in most cases, clinicians have begun to use PD-1 inhibitors for patients with relapse after allogeneic HSCT, with initial reports of both efficacy and significant toxicity (53-60). This experience led to two larger multicenter, retrospective analyses—an American series of 31 patients and a French series of 20 patients (61,62) (*Table 3*). In both series, patients were young (median age 33–37) and the vast majority underwent transplantation for R/R cHL. Among cHL patients, the investigator-assessed ORR to PD-1 blockade was high (79–95%), including higher CR rates (52–54%) than were seen in the R/R setting, suggesting possible synergy of GVT and PD-1 blockade. However, treatment was also associated with high rates of treatment-emergent GVHD (30–55%) including many cases of steroid-refractory GVHD. Across the two studies, 10 of 51 patients died of GVHD-related complications after a median follow-up of 8–12 months (61,62). Risk factors for the emergence of severe GVHD are not yet clear. The French study reported a higher incidence of GVHD for patients with a shorter interval between HSCT and PD-1 therapy and for patients with a prior history of GVHD, however, these associations were not corroborated by the American study (61,62). There are now clinical trials prospectively investigating treatment with PD-1 and PD-L1 inhibitors for relapse after allogeneic HSCT (NCT01822509, NCT02981914, NCT02603419). A preliminary report from the phase 1 JAVELIN study of the PD-L1 inhibitor avelumab included 8 patients treated for relapse after allogeneic HSCT. Six patients achieved a response (1 CR, 5 PRs), however, two patients developed grade 3 liver GVHD which resolved after immunosuppressive therapy and avelumab discontinuation (63). Some of these studies are exploring strategies such as slower dose escalation of PD-1 inhibitors and may also succeed in identifying predictors of response and toxicity. Prior transplant strategies may also affect the risk of treatment-emergent GVHD. A single-center, retrospective study reported low rates of treatment-emergent GVHD for nine patients who received post-transplant cyclophosphamide as GVHD prophylaxis for allogeneic HSCT and were subsequently treated with checkpoint inhibitor for relapse. With a median follow-up of 2 years, only one patient developed treatment-emergent GVHD (42).

Mechanisms of primary and acquired resistance

As immune checkpoint inhibitors are used more widely, there is a growing effort across many cancer types to identify subsets of patients who are most and least likely to benefit from treatment with a specific checkpoint inhibitor. In cHL, 9p24.1 alteration status and PD-L1 expression can identify a subset of patients with the most robust responses to PD-1 inhibitors (12,14), however, this biomarker is not a strong enough discriminant at present to guide clinical decision making. While the tumor microenvironment is critical for the growth and survival of cHL cells, attempts to uncover features of infiltrating immune cells that predict responses to PD-1 inhibitors in cHL have not been successful to date. For example, PD-1 expression on intra-tumoral histocytes and macrophages (12) and interferon-inflammatory immune signature (11) did not predict response to PD-1 therapy, although these efforts may have been limited by small sample sizes.

A better understanding of mechanisms of primary and acquired resistance will be important to better select patients for treatment with PD-1 blockade and to rationally design trials of PD-1 based drug combination. We may learn from progress made in this area in other malignancies. Among melanoma patients treated with a PD-1 inhibitor, a transcriptomic signature in melanoma tumor cells, termed innate anti-PD1 resistance (IPRES), may predict primary resistance to PD-1 therapy (64). The IPRES signature, which is marked by increased expression of genes involved in the regulation of mesenchymal transition, cell adhesion, extracellular matrix remodeling, angiogenesis, and wound healing, has been identified in other solid tumors (64), but has not yet been reported in cHL. Loss of PTEN signaling, which is seen in up to 30% of melanoma tumors, also appears to be associated with decreased T cell infiltration into tumor tissues and primary resistance to PD-1 therapy in patients with melanoma. This finding prompted animal model testing of concurrent treatment with a PI3K-beta inhibitor, which improved the efficacy of both anti-PD1 and anti-CTLA-4 directed therapies, providing a rationale for combination therapy in future clinical trials (65). Finally,

Table 3 PD-1 blockade for relapse of cHL after allogeneic HSCT

	United States (n=31) (61)	France (n=20) (62)
Age at time of HSCT (median)	37	33
Disease		
cHL	29 (94%)	100%
NHL	2 (6%)	0%
Donor type		
MRD	16 (52%)	10 (50%)
MURD	10 (32%)	3 (15%)
MMURD	1 (3%)	3 (15%)
Haplo-identical	4 (13%)	1 (5%)
Double umbilical cord	0 (0%)	3 (15%)
GVHD prior to PD-1 TX	19 (61%)	13 (65%)
On systemic immunosuppressive treatment for GVHD	8 (26%)	0 (0%)
PD-1 Blockade		
Nivolumab	28 (90%)	20 (100%)
Pembrolizumab	3 (10%)	0 (0%)
Median follow-up (days)	217	370
GVHD	17 (55%)	
Acute GVHD	6 (19%)	6 (30%)
Overlap GVHD	4 (13%)	5 (25%)
Chronic GVHD	7 (23%)	0 (0%)
Median day of onset of acute GVHD	14–21	<7
Acute GVHD responsive to steroids	1/10 (10%)	2/6 (33%)
GVHD-related deaths	8 (26%)	2 (10%)
ORR (HL patients only)	79%	95%
CR	54%	42%
PR	25%	52%
PFS	Median 591 days	58.2% (12 months)

HSCT, hematopoietic stem cell transplant; cHL, classical Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; MRD, matched-related donor; MURD, matched-unrelated donor; MMURD, mismatched-unrelated donor; GVHD, graft-versus-host disease; ORR, overall response rate; CR, complete response; PR, partial response.

tumor cell-extrinsic mechanisms can lead to primary resistance to PD-1 therapy. Clinical findings have suggested that the presence of T regulatory cells, myeloid derived suppressor cells, and M2 macrophages correlates with reduced survival in multiple cancer types (66). Furthermore, localization of myeloid derived suppressor cells and M2 macrophages within tumors may predict reduced efficacy of immunotherapy drugs (66). Efforts to eliminate or reprogram these cell populations are underway and targeted therapy with P13K-gamma inhibitors results in a switch to an immunostimulatory transcriptional program, which appears to be synergistic with checkpoint inhibitor therapy in preclinical models (67). Ongoing analyses in cHL may reveal similar or unique mechanisms of primary resistance to anti-PD-1 therapy that may justify the clinical testing of novel combinations.

While responses to PD-1 inhibitors in cHL are durable, eventual progression is seen in the majority of patients; yet the mechanism (or mechanisms) of acquired resistance in cHL are not well understood. Evidence from other tumor types suggests that downregulation of PD-1 or increased expression of alternative checkpoint pathways may contribute to immune escape. In a preclinical model, resistance to anti-CTLA-4 therapy was mediated by increased expression of PD-L1 on melanoma cells (68). In a separate mouse study, increased expression of TIM-3 on lung cancer cells was a common mechanism of immune evasion to anti-PD-1 therapy. Moreover, the addition of an anti-TIM3 antibody following failure of PD-1 blockade was associated with a survival advantage (69). Among four patients with melanoma who progressed after an initial response to PD-1 blockade, alterations in interferon-receptor signaling and the loss of antigen-presenting machinery through a mutation in beta-2 microglobulin (B2M) were identified as mechanisms of acquired resistance. Recent studies in cHL, have identified frequent mutations in B2M and the MHC class II transactivator (CIITA) with associated disruption of expression of MHC class I and class II receptors, respectively (70,71). In a retrospective analysis of 108 patients with cHL, decreased or absent expression of B2M and MHC class I was associated with inferior PFS after induction chemotherapy compared to patients with positive expression of B2M and MHC class I, independent of PD-L1/PD-L2 expression status (72). In contrast, MHC class II expression by RS cells was not significantly associated with PFS following initial treatment. The importance of MHC receptor expression for response to PD-1 blockade has not yet been reported, but abnormalities in antigen presentation could underlie resistance to PD-1 blockade. Investigation in this area and others is ongoing and will provide important guidance for future clinical studies.

Conclusions

Because of near universal alterations in 9p24.1 and PD-1 ligand expression, cHL is uniquely sensitive to PD-1 blockade, with the highest response rates of any tumor type. Within a few years, PD-1 inhibitors have revolutionized the treatment of patients with R/R cHL and have transformed the clinical trial landscape for this disease; yet many challenges remain. Based on efficacy in the R/R setting, PD-1 inhibitors have been incorporated in earlier stages of treatment and in combination with other drugs. An almost infinite number of combinations can be envisioned, but success will be more likely if rational combination partners are selected based on compelling preclinical data. Initial data suggested that PD-1 blockade in the context of allogeneic HSCT has the potential for both synergistic efficacy and toxicity. Here too, careful clinical investigation coupled with correlative and basic science research is needed to optimize treatment approaches. With continued, deep and open collaboration between scientific and clinical investigators across academia and the pharmaceutical industry, the ability to cure more patients with cHL with less toxicity may soon be within our reach.

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