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Cognitive Function and Quality of Life in Vorinostat-Treated Patients after Matched Unrelated Donor Myeloablative Conditioning Hematopoietic Cell Transplantation

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Myeloablative conditioning allogeneic hematopoietic cell transplantation (HCT) puts patients at greater risk for significant cognitive and quality of life decline compared with recipients of reduced-intensity conditioning or autologous HCT. Vorinostat, a histone deacetylase inhibitor, has been shown to have neuroprotective and neurorestorative effects in preclinical models of neurologic diseases. Thus, within the context of a myeloablative conditioning phase II clinical trial of vorinostat combined with tacrolimus and methotrexate for graft-versus-host disease prophylaxis, we conducted an ancillary study to evaluate feasibility of assessing associations between vorinostat and neurocognitive function and quality of life (ClinicalTrials.gov NCT02409134). Nine patients (mean age, 53 years; range, 36 to 66) underwent computerized neuropsychological testing (Cogstate) and completed surveys of mood (Patient Health Questionnaire-9), anxiety (General Anxiety Disorder-7), and quality of life (Functional Assessment of Cancer Therapy–General). Control cohorts from a separate concurrent longitudinal study (19 autologous and 18 allogeneic HCT patients, who matched the vorinostat patients on relevant medical and demographic variables) completed the same test battery. All allogeneic patients received busulfan-based myeloablative conditioning and were transplanted with HLA-matched unrelated donors. The total neurocognitive performance score of vorinostat patients did not change significantly across the study duration (ie, baseline, day 30, day 100, and day 160). Depression, anxiety, and quality of life also did not differ significantly across time. In univariate analyses (analysis of variance), vorinostat-treated patients showed no difference in neurocognitive function or quality of life compared with autologous and allogeneic control subjects. However, when medical variables were accounted for in a linear mixed effects regression model, the total neurocognitive performance of vorinostat-treated patients was comparable with autologous control subjects. Notably, autologous control subjects performed significantly better than allogeneic control subjects (estimate, .64; standard error, .23; $P \leq .01$). Moreover, a smaller percentage of vorinostat-treated patients were classified as mildly, moderately, or severely impaired across neurocognitive domains as well as time points compared with both control cohorts. Thus, vorinostat may have neurorestorative or neuroprotective effects in the HCT setting. Accordingly, we recognize the need for a future, full-scale randomized controlled trial to further examine this hypothesis.

INTRODUCTION

Emerging data suggest that adult recipients of hematopoietic cell transplants (HCT) are at risk of cognitive decline, which can be subtle and transitory or may extend beyond 1 and 5 years post-HCT [1-3]. Although autologous HCT has been associated with little cognitive decline, allogeneic HCT has been associated with acute cognitive decline that persists over time or is delayed, depending on whether it is in the myeloablative or reduced-intensity conditioning setting, respectively [4]. Well-recognized factors contributing to cognitive decline include the neurotoxic effects of chemotherapy, radiation (eg, total body irradiation), immunosuppressive agents, central nervous system infections, or other central nervous system–related complications (eg, posterior reversible

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encephalopathy syndrome) [2]. A major gap in the literature remains the use of neuroprotective or neurorestorative agents in the HCT setting [1–4].

Histone acetylation is an epigenetic modification that has been implicated in the pathophysiology of some neurodegenerative and neuropsychiatric disorders, including depression [5,6]. Indeed, epigenetic mechanisms have been implicated in cognitive decline that is associated with normal aging as well as neurologic disorders, such as Alzheimer disease [7]. Histone acetylation diminishes the electrostatic affinity between histone proteins and negatively charged DNA, thereby promoting gene transcription. In turn, this increased chromatin plasticity is believed to be associated with learning and memory processes, which is facilitated in part by histone acetyltransferases, or "writers," and opposed by histone deacetylases (HDACs), or "erasers" (ie, enhanced by HDAC inhibitors) [8].

Vorinostat, an HDAC inhibitor, has been shown to have neuroprotective and neurorestorative effects in preclinical models of neurologic diseases [9] and also in healthy humans with posttraumatic stress disorder [10,11]. In the current study, which was ancillary to a phase II clinical trial of vorinostat combined with standard graft-versus-host disease (GVHD) prophylaxis after matched unrelated donor myeloablative conditioning HCT, [12] we sought to examine the feasibility of assessing neurocognitive function, depression, anxiety, and quality of life and their associations with vorinostat. To provide a metric for evaluating these associations, we obtained control cohorts of autologous and allogeneic HCT recipients that were matched for relevant transplant and demographic characteristics.

METHODS

Vorinostat-Treated Study Cohort

Patients were eligible for this ancillary study if they met the enrollment requirements of the primary study (ClinicalTrials.gov NCT01790568) [12]. Briefly, eligibility included age ≥ 18 years, diagnosis of hematologic malignancy, candidate for myeloablative conditioning HCT, Karnofsky performance score ≥ 70%, and life expectancy of >6 months. An 8/8 HLA allelic match between an unrelated donor and the recipient at HLA-A, HLA-B, HLA-C, and HLA-DRB1 by high-resolution phenotyping was required. The graft source could be bone marrow or peripheral blood stem cells. Inclusion criteria also included competence in reading, speaking, and understanding English and agreement to the proposed longitudinal assessments. The prespecified administration of vorinostat was between day −10 and day 100 post-HCT. Exclusion criteria were documented evidence of cognitive impairment before enrollment, including diagnoses of dementia, mild cognitive impairment, severe mental illness (diagnosis of schizophrenia or bipolar disorder), or other neurologic illnesses that impact cognition. Patients undergoing a total body irradiation–based conditioning regimen (eg, 1200 cGy) or with a history of prolonged QTc syndrome or who had prior treatment with an HDAC inhibitor (eg, valproic acid) within 30 days were excluded from the study.

Control Cohorts

The control cohorts were derived from cases in a concurrent institutional review board–approved longitudinal neurocognitive study comprised of individuals undergoing either allogeneic (n= 18) or autologous (n=19) HCT. The eligibility criteria for these control subjects were the same as the study population. Participants across all 3 groups were matched for age and gender and were shown via means testing not to differ significantly demographically (Table 1). The conditioning regimens and degree of HLA match between the allogeneic donor and recipient did not differ between the vorinostat-treated and allogeneic control subjects who did not receive vorinostat.

Study Design

The primary phase II GVHD prevention clinical trial enrolled subjects between June 2013 and July 2016 with a target enrollment of 37 patients, as previously published [12]. Vorinostat was administered on day −10 at a dose of 100 mg orally twice daily and continued until day 100 after transplant. Based on the potential neuroprotective effects of vorinostat we conducted an institutional review board–approved pilot ancillary study to examine neurocognitive and self-reported quality of life measures within the setting of the primary prevention trial (Clinicaltrials.gov NCT02409134). Because of a time lag in securing funding for the ancillary study, it was conducted between May 2015 and July 2016. Of the targeted 37 patients from the primary clinical trial, 19 patients had already been accrued, leaving only 18 in the primary clinical trial eligible for the ancillary study when it eventually opened. The ancillary study design included assessment of neurocognitive function and quality of life at 4 time points: before admission to the hospital for HCT (baseline) and days 30, 100, and 160 post-transplant, in conjunction with routine clinical visits. The patient-reported outcomes of quality of life, depression, and anxiety were assessed concurrently and electronically using the Qualtrics (Qualtrics, 333 West River Park Drive, Provo, Utah, 84604) platform on an Apple iPad tablet (Apple Inc., 1 Infinite Loop, Cupertino, CA 95014 USA).

Outcome Measures

The following well-validated measures were used in this study:

1. *Neurocognitive function*: Cogstate [13] is a valid and reliable [14-16] computerized assessment. We selected the battery based on prior HCT studies that indicated the cognitive abilities susceptible to decline among HCT patients: psychomotor (processing) speed, attention, visual learning, visual working memory, visual problem solving/executive functioning, and visual recall (memory) (~17 minutes to complete). Test scores are expressed as *z* scores (mean, 0; standard deviation [SD], 1) standardized by age. Lower scores indicate better performance on tests of processing speed and attention (ie, shorter response time) and visual problem-solving and visual recall (ie, fewer errors). Higher scores indicate better performance (ie, greater accuracy) on tests of visual learning and visual working memory (Supplemental Table 1). For ease of interpretation of the tables and discussion of the findings, we transformed all Cogstate scores so that higher scores indicate better function. We then created a composite total neurocognitive performance summary score, by summing and averaging scores of all six Cogstate tests.
2. *Quality of life:* The Functional Assessment of Cancer Therapy–General (FACT-G) [17] was designed specifically for patients undergoing cancer treatments and evaluates symptoms related to physical, social, emotional, and functional well-being. The FACT-G has been shown to be reliable and valid in this population and has good sensitivity to change over time [18, 19]. Higher scores indicate higher quality of life (27 items; ~6 minutes to complete).
3. *Depression:* The Patient Health Questionnaire-9 [20] has been validated as a diagnostic screening instrument for mood disorders and has sensitivity and specificity for making criteria-based diagnoses of depressive disorders and indicating depression severity [21]. Higher scores indicate worse depression: a score ≥ 10 is indicative of clinically significant depression (9 items; <2 minutes to complete).
4. *Anxiety*: General Anxiety Disorder-7 [22] has been validated as a diagnostic screening instrument for anxiety disorders and has sensitivity and specificity for making criteria-based diagnoses and indicating anxiety severity [23]. Higher scores indicate worse anxiety: a score ≥ 10 is indicative of clinically significant anxiety (7 items; <2 minutes to complete).

Statistical Analyses

Stata 15 [24] and SPSS 24 [25] were used to perform the statistical analyses. Demographic and clinical characteristics were described using means, SDs, ranges, frequencies, and percentages, as appropriate. To examine changes over time at the univariate level, repeated-measures analysis of variance with Bonferroni correction for multiple comparisons was used. To determine the degree to which the 3 cohorts differed from published norms of cancer patients and the general population, Bonferroni-corrected 1-sample *t*-tests were used.

To investigate determinants of neurocognitive function and quality of life over time, we fitted a series of linear mixed-effects regression models [26]. Linear mixed-effects regression models extend linear regression models by accounting for the repeated measurements structure in the data that would violate the independence assumption of linear regression. This is accomplished through the use of a random intercept per participant allowing for the existence of within-subject correlation across time.

Table 1
Descriptive Statistics for Demographic and Medical Variables

	Vorinostat (n = 9)		Allogeneic (n = 18)		Autologous (n = 19)	
Demographic variables						
	M (SD)	*Range*	*M (SD)*	*Range*	*M (SD)*	*Range*
Age, yr*	52.56 (11.18)	36-66	58.28 (11.54)	27-72	54.95 (8.40)	40 -69
Education, yr†	13.22 (2.11)	10-16	14.39 (2.75)	11-18	14.63 (2.43)	10-20
	N	*(%)*	*N*	*(%)*	*N*	*(%)*
Age ≥ 65 yr	*2*	(22.2)	*4*	(22.2)	*2*	(10.5)
Male gender*	5	(55.6)	9	(50.0)	10	(52.6)
Medical variables						
	M (SD)	*Range*	*M (SD)*	*Range*	*M (SD)*	*Range*
Inpatient days to day 100*,‡	18.56 (8.79)	14-41	16.39 (2.89)	12-21	15.0 (3.40)	12-24
Total vorinostat, mg†	13594.4 (4067.9)	10150-22200	0		n/a	
Average vorinostat, mg†,§	139.07(28.95)	93.70-200	0		n/a	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*
Steroids used*	*3*	(33.3)	*5*	(27.8)		0 (0)
Indication for HCT*						
AML	7	(77.8)	11	(61.1)		
MDS	2	(22.2)	5	(27.8)		
CML			2	(11.1)		
MM					11	(57.9)
HL					1	(5.3)
NHL					7	(36.8)
Comorbidity index*						
Low	2	(22.2)	4	(22.2)	8	(42.1)
Intermediate	5	(55.6)	4	(22.2)	2	(10.5)
High	2	(22.2)	10	(55.6)	9	(47.4)
Risk status*						
Low	5	(55.6)	11	(61.1)	12	(63.2)
Intermediate	3	(33.3)	0	(0)	2	(10.5)
High	1	(11.1)	7	(38.9)	5	(26.3)
Cell source*						
BM	5	(55.6)	4	(22.2)	0	(0)
PBSC	4	(44.4)	14	(77.8)	19	(100)
GVHD*						
Acute	3	(33.3)	5	(27.8)		n/a

M indicates mean; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; CML, chronic myelogenous leukemia; MM, multiple myeloma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; BM, bone marrow; PBSC, peripheral blood stem cell.

* Source was medical record.

† Source was self-report.

‡ Post-HCT, ie, excluding days spent conditioning.

§ Average daily dose.

For each neurocognitive function outcome (each of the 6 neurocognitive domains and the composite of all 6), we fitted a linear mixed-effects regression model predicting the outcome based on group membership (vorinostat-treated versus allogeneic control versus autologous control) and time point (which allows for how outcomes change). A group-by-time interaction was included to allow the change over time to differ between groups. In addition, a number of clinically significant variables were included to adjust for any additional uncontrolled heterogeneity between the groups that the matching was insufficient to address: an indicator of age ≥ 65, disease risk status, cell source, presence of any steroid use, and length of hospital stay through day 100 (as a proxy for treatment course complications).

For quality of life a linear mixed-effects regression model was again used with group membership and time and their interaction. The additional clinical variables were an indicator of age ≥ 65, gender, comorbidity index, presence of any steroid use, years of education, depression, and composite total neurocognitive performance.

For both neurocognitive function and quality of life, covariates were included based on their clinical relevance and whether their inclusion improved the model fit, as indicated by the Akaike information criterion [27].

RESULTS

Vorinostat-Treated Patient Cohort

Patient characteristics

Between May 2015 and July 2016, 13 patients (72%) enrolled in the ancillary study and 5 declined, due to perceived participant burden (ie, testing length of time). Of the 13 who enrolled, all completed baseline testing, 10 completed day 30 testing, 9 completed day 100 testing, and 8 completed day 160 testing (Figure 1). The baseline characteristics of these 9 patients are provided in Table 1. The mean age of the vorinostat-treated cohort was 53 years (range, 36 to 66), most (78%) had intermediate-to-high comorbidity index, 56% were men, and 56% had at least some college education. Indications for HCT were acute myelogenous leukemia (n = 7) or myelodysplastic syndrome (n = 2).

Neurocognitive function

All neurocognitive outcomes were reported as *z*-scores, which are equivalent to SDs relative to a mean of 0, based on age. Mean baseline neurocognitive function was within one-half an SD of the standardization mean of 0 on all subtests (ie, within normal limits). The trajectories of subtests differed: Processing speed, attention and visual problem-solving improved by day 30 but declined by day 100, whereas the opposite pattern was evident in visual learning, working memory, and visual recall. By day 160 (ie, 2 months off vorinostat) processing speed, attention, visual learning, and visual recall

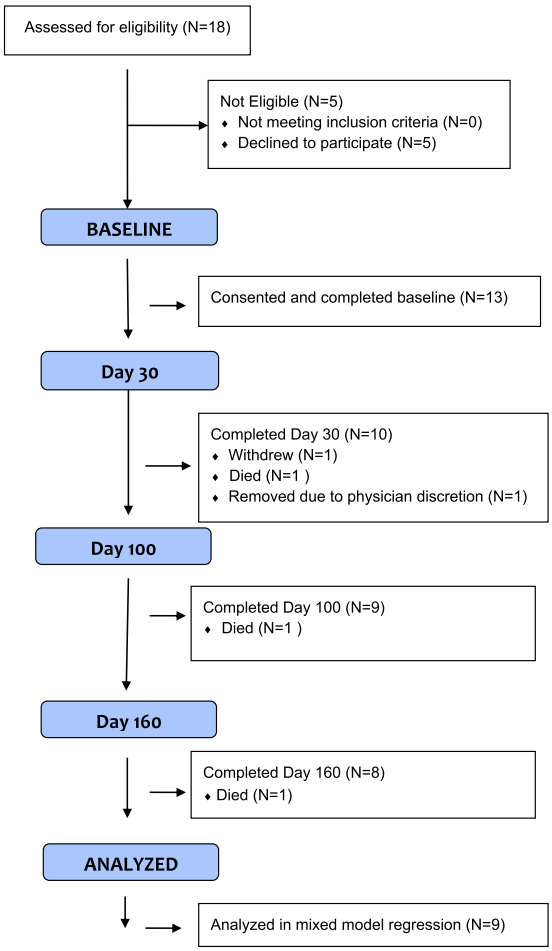

Figure 1. CONSORT diagram.

declined relative to day 100, but working memory and problem-solving improved. However, total neuropsychological performance changed little and not to a statistically significant degree across the study duration (ie, baseline to day 160) (Table 2).

Psychological function

In repeated-measures analysis of variance depression, anxiety, and quality of life scores did not significantly differ across time (ie, baseline, day 30, day 100, and day 160) (Table 3).

Comparison with Autologous and Allogeneic Control Cohorts

Autologous and allogeneic control patient characteristics

Nineteen control patients underwent autologous HCT and 18 control patients underwent allogeneic matched unrelated donor HCT without vorinostat. There were no statistically significant differences in age, gender, years of education, disease risk status, or comorbidity index across the 3 cohorts (ie, vorinostat-treated, autologous control, allogeneic control). The overall population mean age was 56 years (range, 27 to 72). Baseline characteristics of the 3 cohorts are detailed in Table 1.

Neurocognitive function comparison across cohorts

At the univariate level the 3 cohorts did not differ significantly in neurocognitive function (Table 2). As shown in Figure 2A to F, vorinostat-treated patients exhibited no deficits $\geq$ 1 SD in visual problem-solving and visual recall at any time points, in contrast to autologous and allogeneic control subjects. At day 30 vorinostat-treated patients showed no deficits in processing speed or attention, whereas, again, autologous and allogeneic control subjects did show deficits. Further, at day 100, vorinostat-treated patients were less impaired (ie, mild only) in any domain, whereas autologous or allogeneic control subjects showed moderate-to-severe deficits.

To investigate determinants of neurocognitive function across the 3 cohorts and over time, a linear mixed-effects regression model was fitted to each of the 6 neurocognitive outcomes and the composite of all 6 tests (total neurocognitive performance). At baseline, day 30, and day 100 the total neurocognitive performance of the autologous control cohort was significantly better than the allogeneic control cohort but did not differ from the vorinostat-treated cohort (Table 4), when accounting for all covariates listed both in Statistical Analyses above and in Table 5. Similar findings were exhibited in processing speed, attention, visual learning, and visual working memory at day 30 (Table 4). Further, older age ($\geq$65 years) predicted worse visual working memory to the extent of nearly a full SD compared with those $<$ age 65 years (Table 5).

Psychological function comparison across cohorts

At the univariate level the 3 cohorts did not differ significantly in depression, anxiety, or quality of life (Table 3). To investigate determinants of quality of life across the 3 cohorts and over time, a linear mixed-effects regression model was fitted to the FACT-G total score. We found no significant differences between groups at any of the time points (ie, after covariate-adjusted pairwise comparisons of the group-by-time interaction; Table 6). However, when all covariates were accounted for, depression and high comorbidity scores predicted worse quality of life across cohorts

DISCUSSION

Allogeneic HCT patients, particularly those who receive myeloablative conditioning, are at significant risk for cognitive impairment with progressive decline and limited recovery over time [28-30]. It was recently reported that allogeneic HCT patients with global cognitive deficit at 3 years post-HCT were at 10-fold higher odds of not returning to work, suggesting that cognitive functioning is critical for integration into society [4]. Further, as highlighted by Sharafeldin et al. [4], monitoring cognitive function in the post-HCT setting is imperative because it may enable earlier identification of high-risk patients and facilitate interventions, such as neurocognitive training [31–33].

We previously reported that vorinostat was safe and feasible to administer in the related donor reduced-intensity conditioning setting and resulted in lower incidence of acute GVHD (primary endpoint) [34]. No deaths were related or attributable to vorinostat treatment. Furthermore, no drug-related toxic effects arose that warranted discontinuation of vorinostat. Thus, it was logical to expand the use of vorinostat for GVHD prevention in the higher risk, unrelated donor myeloablative conditioning setting [12]. Recognizing the risk for cognitive impairment in patients undergoing myeloablative HCT along with neuroprotective and neurorestorative potential of HDAC inhibitors, we sought to explore the impact of vorinostat on cognitive function post-HCT.

The feasibility of this investigation was attested to by the fact that 72% of eligible participants enrolled in the primary GVHD prevention trial were willing to comply with prospective, longitudinal assessments of neurocognitive function and quality of life during the first 160 days post-transplant. Only 1 participant withdrew after enrollment because of burden.

Table 2
Descriptive Statistics for Neurocognitive Variables (*z* scores; higher more desirable)

	Vorinostat (n = 9)	Allogeneic (n = 18)	Autologous (n = 19)
	M (SD)	M (SD)	M (SD)
Psychomotor speed			
Baseline	−.21 (.88)	−.33 (.96)	.20 (.92)
Day 30	−.06 (.59)	−.95 (1.04)	.20 (.99)
Day 100	−.56 (.70)	−.39 (.69)	.15 (.97)
Day 160	−.63 (.76)		
Attention			
Baseline	−.42 (1.27)	−.40 (1.19)	.17 (1.11)
Day 30	−.17 (.43)	−.73 (1.05)	−.09 (1.28)
Day 100	−.36 (.69)	−.15 (.97)	.25 (1.00)
Day 160	−.48 (.85)		
Visual learning			
Baseline	−.10 (.78)	−.68 (1.07)	−.24 (1.03)
Day 30	−.22 (.98)	−.67 (1.55)	.08 (.93)
Day 100	−.01 (1.0)	−.39 (1.15)	−.18 (.93)
Day 160	−.56 (.92)		
Working memory			
Baseline	.17 (.82)	−.41 (.78)	.11 (.92)
Day 30	−.11 (.97)	−.51(1.19)	.21 (.96)
Day 100	.06 (.84)	−.43 (.89)	−.05 (1.04)
Day 160	.48 (.72)		
Visual problem-solving			
Baseline	.44 (.59)	−.23 (1.04)	−.15 (1.02)
Day 30	.57 (.52)	.02 (.95)	.21 (.83)
Day 100	.40 (.60)	.20 (.77)	.42 (.90)
Day 160	.55 (.77)		
Visual memory			
Baseline	.50 (.66)	−.38(1.78)	.04 (1.38)
Day 30	.36 (.68)	−.02 (1.53)	.50 (.97)
Day 100	.80 (.90)	.78 (.67)	.53 (1.08)
Day 160	.60 (1.04)		
Total neurocognitive performance			
Baseline	.06 (.48)	−.39 (.91)	.02 (.65)
Day 30	.06 (.31)	−.46 (.78)	.19 (.62)
Day 100	.05 (.34)	−.04 (.57)	.19 (.69)
Day 160	−.01 (.55)		

Autologous and allogeneic control subjects were not assessed at day 160.

Contributing to good patient retention was our use of the brief, repeatable, low-patient-burden neurocognitive battery, Cogstate, which facilitated monitoring over time, consistent with recommended best practices. Further, the brevity of Cogstate made it cost-effective compared with traditional neuropsychological assessments, which can be burdensome to providers with regards to time, cost, resources, and personnel. Additionally, because Cogstate is efficiently and accurately computer-administered, it protects against administrator drift or error, making it convenient for use in multicenter studies.

In the current study, as indicated by the total neurocognitive performance score and 4 of 6 Cogstate domains at day 30, vorinostat-treated patients' neurocognitive performance was similar to that of the autologous control cohort. However, allogeneic control subjects not treated with vorinostat experienced significant neurocognitive dysfunction compared with autologous control subjects. This pattern of findings is consistent with the recent Kelly et al. study [2] showing that cognitive functioning was significantly impaired in myeloablative HCT but generally spared in autologous HCT recipients. In addition, compared with both control cohorts, a smaller percentage of the vorinostat-treated cohort scores were classified as mildly, moderately, or severely impaired across domains and time points. Thus, fewer vorinostat patients would be in need of other forms of intervention, such as compensatory skill training or cognitive retraining.

Interestingly, we found that older age (≥65 years) was a significant predictor of worse visual working memory, to the extent of nearly a full SD (.9 SD), regardless of study cohort (ie, vorinostat-treated, autologous control subjects, allogeneic control subjects). This finding is consistent with recent studies of cognitive impairment in older patients [4,35]. Because of the potential impact of steroid use on neurocognitive function, we also included it as a covariate in our models. Although Scherwath et al. [29] did not find an association between steroid use and cognition, Jim et al. [28] reported a lower likelihood of cognitive recovery with steroid use. In the current study steroid use was not associated with cognitive performance. We recognize that discrepancies between studies are likely related to sample size and different covariates assessed, including other pharmacologic interactions that are not being account for. Nonetheless, further exploration of the age effect as well as role of GVHD and steroid use is warranted when assessing neurocognitive function in the post-HCT setting.

Despite the reduction in grades II to IV acute GVHD in vorinostat-treated patients [12], depression, anxiety, and quality of life assessments were not significantly different from the control cohorts. There are several explanations for this. First, although we matched cohorts on several key medical and demographic variables, this was not a randomized trial. Second, our follow-up period was short and possibly did not provide enough time to detect significant differences in these measures. For example, if cognition is protected in subtle ways by vorinostat, longer follow-up may reveal that return to role and work functions may be differentially restored in myeloablative conditioned allogeneic HCT recipients who received

Table 3
Descriptive Statistics for Depression, Anxiety, and Quality of Life

	Vorinostat (n = 9)		Allogeneic (n = 18)		Autologous (n = 19)	
	M (SD)	Range	M (SD)	Range	M (SD)	Range
Depression*						
Baseline	5.11 (3.89)	0-12	5.11 (6.13)	0-27	3.57 (3.19)	0-11
Day 30	7.11 (5.21)	0-17	6.50 (6.23)	0-24	4.89 (3.18)	0-11
Day 100	4.67 (2.92)	2-10	4.12 (3.72)	0-11	4.58 (4.98)	0-19
Day 160	3.50 (3.96)	3-12				
Anxiety†						
Baseline	2.78 (3.49)	3.72	5.11 (4.15)	0-21	2.26 (2.51)	0-8
Day 30	1.89 (3.02)	0-8	2.28 (3.92)	0-13	1.74 (2.31)	0-7
Day 100	.44 (.88)	0-2	.82 (1.18)	0-4	2.05 (3.21)	0-11
Day 160	.63 (1.19)	0-3				
Quality of life‡						
Baseline	78.26 (16.46)	53-100	82.75 (14.04)	49-100	82.53 (12.27)	60-104
Day 30	76.83 (15.34)	53-99	77.07 (11.59)	54-93	81.75 (14.29)	62-105
Day 100	79.41 (14.10)	58-101	86.45 (11.68)	67-105	84.29 (17.22)	38-106
Day 160	79.48 (17.14)	59-103				

At no time point did any of the cohorts differ significantly from published norms of cancer patients and the general population.

* Lower depression (Patient Health Questionnaire-9) scores are more desirable: Scores of 5, 10, 15 and 20 represent thresholds of mild, moderate, moderately severe, and severe depressive symptoms, respectively. Published means of cancer patients = 5.26 and general population = 3.30 (Hinz et al., 2016).

† Lower anxiety (General Anxiety Disorder-7) scores are more desirable: Scores of 5, 10, and 15 represent thresholds of mild, moderate, and severe anxiety symptoms, respectively. Published means of cancer patients = 5.42 (Ng et al., 2017) and general population in primary care = 4.75 (Jordan et al., 2017)

‡ Higher quality of life (FACT-G) scores are more desirable; Published means of US ambulatory cancer patients = 79.3 and general population = 80.1 (Pearman et al., 2014).

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vorinostat versus those who did not. Third, the sample size was too small to detect significant differences with multiple comparisons at the univariate level (ie, across 3 different groups and multiple time points). Nevertheless, our analyses show that regardless of group (cohort) and time, quality of life was negatively impacted by depression and physical comorbidity. These findings have important clinical and research implications in light of recent reports of correlations between depression and perceived physical functioning and post-HCT health outcomes [36–38]. Thus, future well-designed clinical trials should also include longitudinal assessments of depression.

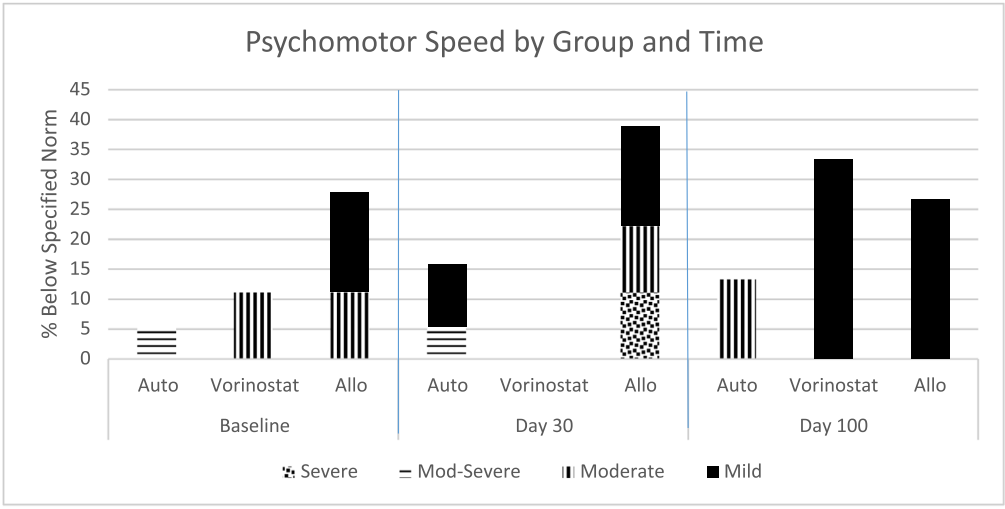
As highlighted above, we recognize the limitations of the current study, namely lack of randomization, short longitudinal follow-up, and small sample size. Further, we recognize the inherent biases afforded by single-center study designs. Importantly, HCT studies investigating the suspected mediating or moderating factors of HCT-related cognitive dysfunction are compounded by morbidity and mortality of HCT recipients that lead to missing data, study attrition, and possible survivor biases, in the sense that survivors are likely to be healthier and less impaired than patients who do not complete longitudinal studies. Well-designed, larger, multicenter studies will provide more power to potentially detect important predictors, whether deleterious, neuroprotective, or neurorestorative.

The current study has several notable strengths. First, to our knowledge, this was the first study to examine the potential neurocognitive and psychological well-being effects of a pharmaceutical agent within the context of a prospective HCT clinical trial (ie, reducing GVHD). Our findings make a tentative and preliminary contribution to the search for interventions for cognitive decline after HCT, a quest in which prospective randomized controlled trials of pharmacologic, compensatory behavioral skill training, or computer-based cognitive training are conspicuous in their absence in this patient population [1,2]. The advantages of vorinostat are that it has promise in the prophylaxis of GVHD in allogeneic HCT [12,34] on the one hand and has demonstrated neuroprotective and neurorestorative effects in basic research in murine models of neurologic disorders [9] and in medically healthy humans with anxiety [10] on the other.

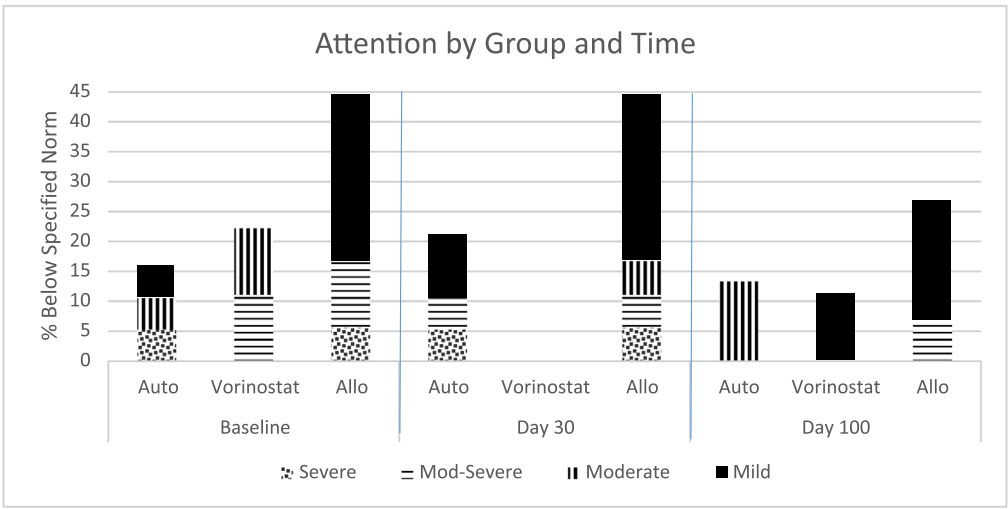
Second, although not gold standard, our use of matched control subjects who received the same battery of instruments enabled exploration of the neurocognitive impact of vorinostat and its effects on quality of life. Despite our small sample size we were still able to perform a multifactorial analysis of determinants of quality of life that included neurocognitive function and depression along with other demographic and medical determinants. Third, the computerized battery we used, Cogstate, is particularly well suited to detect and monitor mild dysfunction over time because alternative forms are built into the battery to mitigate any practice effects. This addresses limitations noted by Sharafeldin et al. [4] that the traditional neuropsychological battery they used was better suited to detect moderate-to-severe brain damage rather than the subtle changes likely to be seen in HCT survivors. Thus, the Cogstate battery with its distinctive psychometrics has clinical utility to address best practice recommendations to monitor patients and evaluate neuropsychological function in patients with cognitive complaints [2]. Finally, the use of linear mixed models in our analyses allowed for multiple variables, at multiple time points, in multiple cohorts, permitting investigation of repeated measures while controlling for autocorrelation among each of the instances of the repeated measures.

In summary, we found that vorinostat-treated patients performed similarly to autologous control subjects in several neurocognitive domains. Allogeneic control subjects who did not receive vorinostat performed worse than autologous control subjects, consistent with the published literature [4]. We

A. Psychomotor (Processing) Speed: Rates of Mild – Severe Impairment



B. Attention: Rates of Mild – Severe Impairment



C. Visual Learning: Rates of Mild – Severe Impairment

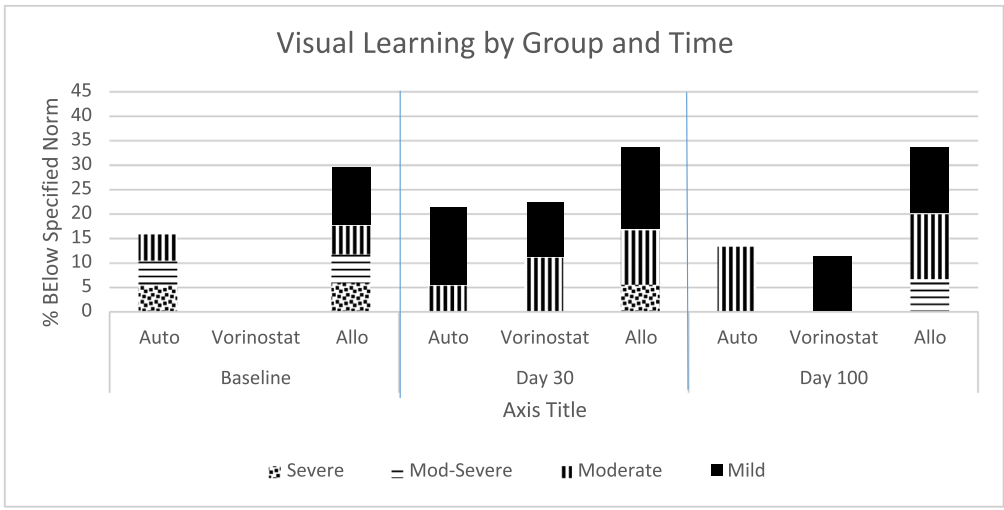
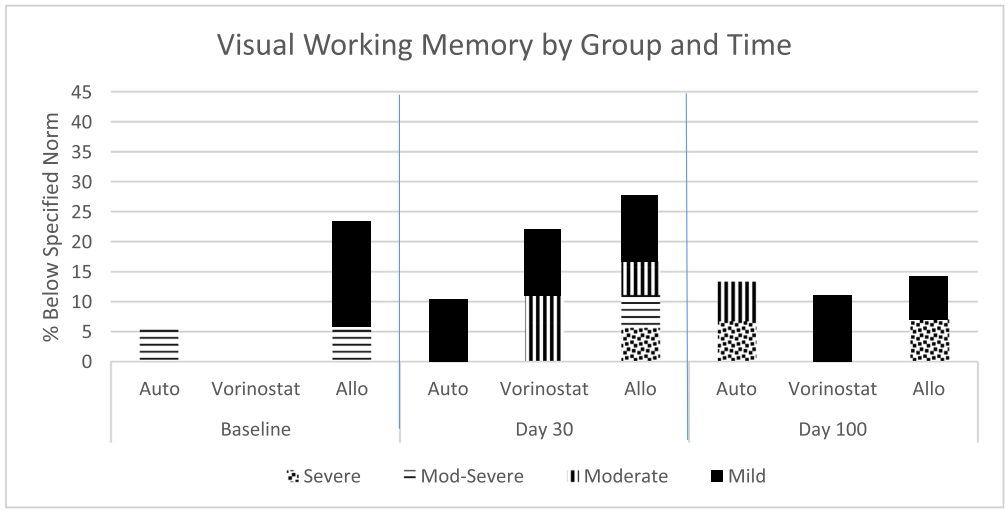
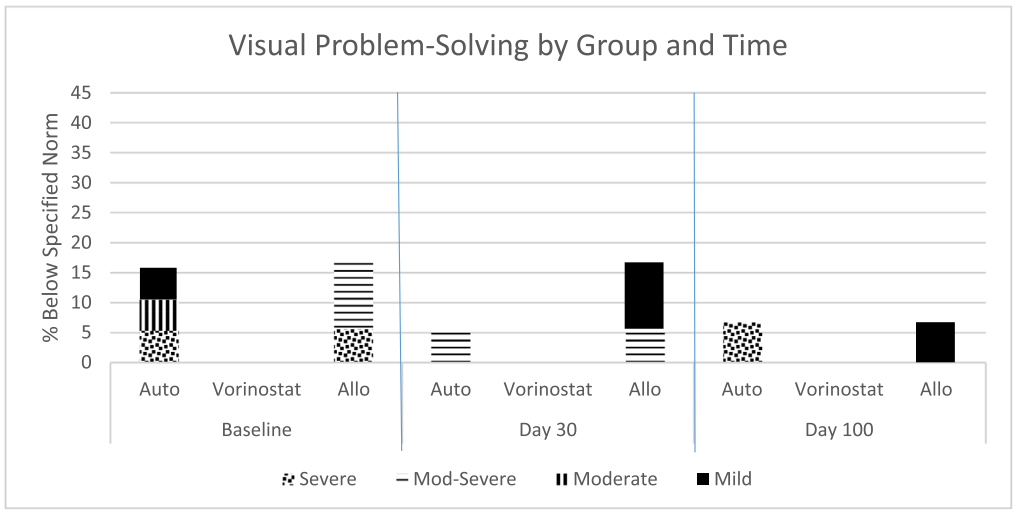


Figure 2. Rates of mild to severe impairment in neurocognitive domains compared across cohorts. To present comparative neurocognitive function across the 3 cohorts, data were stratified according to the percent of each cohort whose scores fell below the normative population mean by 1.0 SD (ie, mild impairment; equivalent to the 16th percentile), 1.5 SD (ie, moderate impairment; equivalent to the 7th percentile), 2.0 SD (ie, moderate-severe impairment; equivalent to the 2nd percentile) and 2.5 SD (ie, severe impairment; below the 1st percentile).

D. Visual Working Memory: Rates of Mild – Severe Impairment



E. Visual Problem-Solving: Rates of Mild – Severe Impairment



F. Visual Recall: Rates of Mild – Severe Impairment

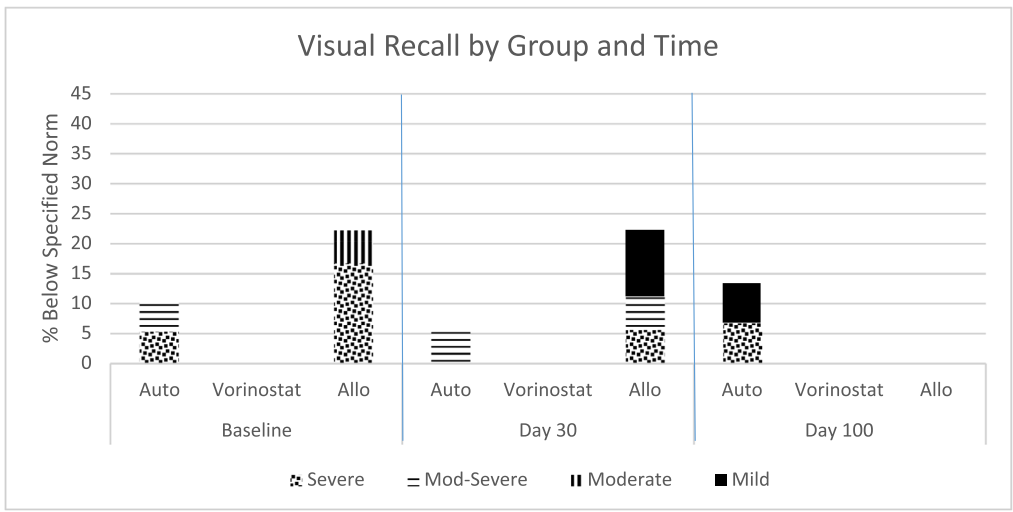


Figure 2. (Continued)

Table 4
Neurocognitive Performance: Each Estimate Is the Predicted Difference between the 2 Groups at the Indicated Time Point, Obtained from the Mixed Effects Regression Model that Adjusts for the Covariates Described in the Statistical Analyses Section

Comparison	Visual Processing Speed Estimate (SE) *P*	Visual Attention Estimate (SE) *P*	Visual Learning Estimate (SE) *P*	Visual Working Memory Estimate (SE) *P*	Visual Problem-Solving Estimate (SE) *P*	Visual Recall Estimate (SE) *P*	Total Neurocognitive Performance Estimate (SE) *P*
Baseline							
Allo vs. Vorinostat	.14 (.39)	.38 (.43)	−.65 (.44)	−.60 (.38)	−.57 (.43)	−.87 (.51) †	−.35 (.29)
Auto vs. Vorinostat	.75 (.42) †	1.07 (.46) *	−.31 (.47)	−.26 (.40)	−.49 (.47)	−.27 (.54)	.08 (.31)
Auto vs. Allo	.62 (.31) *	.69 (.35) *	.34 (.35)	.34 (.30)	.08 (.34)	.60 (.40)	.43 (.23) †
Day 30							
Allo vs. Vorinostat	−.65 (.39) †	−.24 (.43)	−.51 (.44)	−.36 (.38)	−.47 (.43)	−.27 (.51)	−.42 (.29)
Auto vs. Vorinostat	.58 (.42)	.46 (.46)	.18 (.47)	.15 (.40)	−.28 (.47)	.27 (.54)	.22 (.31)
Auto vs. Allo	1.23 (.31) ***	.70 (.35) *	.69 (.34) *	.51 (.30) †	.19 (.34)	.54 (.40)	.64 (.23) **
Day 100							
Allo vs. Vorinostat	.22 (.40)	.28 (.45)	−.52 (.45)	−.48 (.40)	−.35 (.43)	−.17 (.52)	−.19 (.29)
Auto vs. Vorinostat	1.08 (.43) **	1.03 (.47) *	−.12 (.48)	−.25 (.41)	−.10 (.47)	−.16 (.55)	.26 (.32)
Auto vs. Allo	.86 (.33) **	.75 (.37) *	.40 (.38)	22 (.34)	.25 (.35)	.00 (.44)	.45 (.25) †

Higher scores are more desirable; Total neurocognitive performance is a composite, ie, the average of all 6 subtests; SE indicates standard error; Allo, allogeneic; Auto, autologous.
† $P \leq .10$; * $P \leq .05$, ** $P \leq .01$; *** $P \leq .001$.

Table 5
Mixed Effects Models Showing Determinants of Total Neurocognitive Performance: Medical Covariates Adjusted for Group-by-Time Interaction Presented in Table 4

Covariate	Visual Processing Speed Estimate (SE) *P*	Visual Attention Estimate(SE) *P*	Visual Learning Estimate(SE) *P*	Visual Working Memory Estimate (SE) *P*	Visual Problem Solving Estimate(SE) *P*	Visual Recall Estimate(SE) *P*	Total Neurocognitive Performance Estimate(SE) *P*
Age[a]							
Older, 65+	−.00 (.29)	−.39 (.33)	−.70 (.32) *	−.87 (.25) ***	−.22 (.36)	.17 (.38)	−.34 (.23)
Risk status[b]							
Intermediate	.47 (.36)	.23 (.39)	.40 (.40)	.09 (.30)	.07 (.44)	.04 (.47)	.22 (.28)
High	−.05 (.25)	−.25 (.27)	.68 (.27) *	−.17 (.21)	−.28 (.29)	−.01 (.32)	−.01 (.19)
Steroid use[c]							
Yes	.37 (.30)	.51 (.33)	.10 (.33)	.08 (.25)	.42 (.36)	.65 (.39) †	.37 (.23)
Cell source[d]							
PBSC	−.18 (.33)	−.48 (.36)	.21 (.37)	.29 (.28)	.13 (.40)	.11 (.43)	−.02 (.26)
Inpatient days[e]	.01 (.02)	−.04 (.03) †	−.02 (.03)	.01 (.02)	−.01 (.02)	−.02 (.03)	−.01 (.02)
Wald χ^2	29.34 **	23.71 *	20.03	26.92 *	15.68	23.15 *	19.68

Higher scores are more desirable; Total neurocognitive performance is a composite, ie, the average of all 6 subtests.
Reference groups: [a] <65 years; [b] Low risk; [c] No steroids; [d]Bone marrow; [e] Post-HCT days inpatient.
† $P \leq .10$; * $P \leq .05$, ** $P \leq .01$; *** $P \leq .001$.

Table 6
Mixed-Effects Model Showing Determinants of Quality of Life: Group, Time, Group-by-Time Interaction, Demographics, Medical, and Psychological Variables

Covariate	FACT-G Estimate (SE) *P*	
Group [a]		
Autos	-.34 (4.80)	
Allos	5.16 (4.42)	
Time [b]		
Day 30	1.63 (3.23)	
Day 100	.47 (3.20)	
Group by time		
Autos by day 30	-.41 (3.89)	
Autos by day 100	2.73 (4.01)	
Allos by day 30	-6.24 (3.95)	
Allos by day 100	1.16 (4.08)	
Age over 65 [c]		
Older, 65+	−.37 (3.47)	
Gender [d]		
Female	−.07 (2.74)	
Education	.50 (.57)	
Comorbidity index [e]		
Intermediate	-5.21 (4.07)	
High	-6.01(3.12)	*
Steroids used [f]		
Yes	-2.08 (3.98)	
Depression	-1.53 (.22)	***
Composite neurocognition	.03 (1.48)	
Wald χ^2	85.19	****

Higher score is more desirable and indicates better quality of life.
Reference groups: [a] Vorinostat; [b] Baseline; [c] < 65 years [d] Male [e] Low; [f] No steroids used.
*$P \leq .05$, **$P \leq .01$;***$P \leq .001$; ****$P \leq .0001$

recognize the limitations of our study. Nonetheless, our study indicates the feasibility of including cognitive and quality of life assessments within primary GVHD clinical trials, and we encourage investigators to include these in future study designs. A full-scale, adequately powered, randomized controlled trial is needed to further examine the hypothesis that vorinostat may have neurorestorative or neuroprotective effects in the HCT setting.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.09.015.

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