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Association of Antiepileptic Medications with Outcomes after Allogeneic Hematopoietic Cell Transplantation with Busulfan/Cyclophosphamide Conditioning

Jeannine S. McCune[1,18,*], Tao Wang[2], Khalid Bo-Subait[3], Mahmoud Aljurf[4], Amer Beitinjaneh[5], Joseph Bubalo[6], Jean-Yves Cahn[7], Jan Cerny[8], Saurabh Chhabra[9], Aaron Cumpston[10], L. Lee Dupuis[11], Hillard M. Lazarus[12], David I. Marks[13], Richard T. Maziarz[6], Maxim Norkin[14], Tim Prestidge[15], Shin Mineishi[16], Maxwell M. Krem[17], Marcelo Pasquini[3], Paul J. Martin[1]

[1] *Clinical Research Division, Fred Hutchinson Cancer Research Center and Department of Medicine, University of Washington, Seattle, WA, USA*
[2] *Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI, USA*
[3] *CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI*
[4] *Adult HSCT Program, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[5] *Department of Medicine, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL, USA*
[6] *Department of Medicine, Oregon Health and Science University Hospital, Portland, OR, USA*
[7] *Department of Medicine, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France*
[8] *Department of Medicine, University of Massachusetts Memorial Medical Center, Worcester, MA, USA*
[9] *Department of Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI*
[10] *Division of Oncology, West Virginia University Hospitals, Morgantown, WV, USA*
[11] *The Hospital for Sick Children and Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada*
[12] *Department of Medicine, Case Western Reserve University, Cleveland, OH, USA*
[13] *Bristol Haematology and Oncology Centre, University Hospitals Bristol NHS Foundation Trust, Bristol, UK*
[14] *Department of Medicine, University of Florida College of Medicine, Gainesville, FL, USA*
[15] *Blood and Cancer Centre, Starship Child Health, Central Auckland, New Zealand*
[16] *Department of Medicine, Penn State Hershey Medical Center, Hershey, PA, USA*
[17] *Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, KY, USA*
[18] *Department of Population Sciences, City of Hope, Duarte, CA, USA*

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A B S T R A C T

High-dose busulfan (BU) followed by high-dose cyclophosphamide (CY) before allogeneic hematopoietic cell transplantation (HCT) has long been used as treatment for hematologic malignancies. Administration of phenytoin or newer alternative antiepileptic medications (AEMs) prevents seizures caused by BU. Phenytoin induces enzymes that increase exposure to active CY metabolites in vivo, whereas alternative AEMs do not have this effect. Lower exposure to active CY metabolites with the use of alternative AEMs could decrease the risk of toxicity but might increase the risk of recurrent malignancy after HCT. Previous studies have not determined whether outcomes with alternative AEMs differ from those with phenytoin in patients treated with BU/CY before allogeneic HCT. We studied a cohort of 2155 patients, including 1460 treated with phenytoin and 695 treated with alternative AEMs, who received BU/CY before allogeneic HCT between 2004 and 2014. We found no differences suggesting decreased overall survival or relapse-free survival or increased risks of relapse, nonrelapse mortality, acute or chronic graft-versus-host disease, or regimen-related toxicity associated with the use of alternative AEMs compared with phenytoin. The risk of dialysis was lower in the alternative AEM group than in the phenytoin group. Alternative AEMs are safe for prevention of seizures after BU administration and can avoid the undesirable toxicities and drug interactions caused by phenytoin.

INTRODUCTION

High-dose busulfan (BU) is often used to decrease the burden of malignant cells in the recipient before allogeneic hematopoietic cell transplantation (HCT). BU administration can cause seizures [1]. Originally, phenytoin was the

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* Correspondence and reprint requests: Jeannine S. McCune, PharmD, City of Hope, Beckman Research Institute, 1500 E Duarte Road, Lippman-Graff B125, Duarte, CA 91010.
E-mail addresses: jmccune@coh.org, jmccune@uw.edu (J.S. McCune).

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antiepileptic medication (AEM; formerly referred to as antiepileptic drug) most frequently used to prevent BU-induced seizures. Phenytoin is well known as a strong inducer of hepatic drug-metabolizing enzymes, specifically the cytochrome P450 (CYP) enzymes CYP2B6, CYP2C, and CYP3A and the UDP glucuronosyltransferases (UGTs) [1]. Enzyme induction occurs within 24 hours after administration of phenytoin and persists for at least 1 week after discontinuation of phenytoin [2]. More recently, newer alternative AEMs, such as levetiracetam, have been increasingly used as a replacement for phenytoin to prevent BU-induced seizures. Compared with phenytoin, these alternative AEMs have 2 advantages: fewer potential drug interactions because they do not induce CYPs or UGTs, and fewer toxicities [3].

BU is often used in combination with high-dose cyclophosphamide (CY) as a conditioning regimen before allogeneic HCT. CY is a prodrug with multiple metabolites (see Supplementary Figure 1 for pharmacokinetic schema of CY and its metabolites) [4]. Among these, 4-hydroxycyclophosphamide (4HCY) is critical because it is transported intracellularly and spontaneously decomposes to phosphoramide mustard, which covalently cross-links DNA. The 4HCY metabolite carboxyethylphosphoramide mustard (CEPM) is the predominant plasma metabolite after CY administration. Variability in the area under the plasma concentration time curve (AUC) of CY, 4HCY, or other metabolites may account for interpatient differences in the efficacy and toxicity of CY [2,4-6].

Rezvani et al [4] compared the pharmacokinetics of CY, 4HCY, and CEPM in patients treated either with CY followed by targeted BU (CY/^{T}BU) or with ^{T}BU followed by CY (^{T}BU/CY). To prevent seizures, both groups received phenytoin at the start of BU administration. Phenytoin administered before CY accounts for the greater 4HCY AUC in the ^{T}BU/CY group, whereas phenytoin given in conjunction with BU had no effect on CY metabolism in the CY/^{T}BU group [4,6]. Compared with the CY/^{T}BU group, the ^{T}BU/CY group had a ~.48-fold lower CY AUC and a 1.7-fold higher 4HCY AUC. In patients treated with CY/^{T}BU, higher 4HCY AUCs were associated with a statistically significant greater risk of mortality [4]. Both groups received ^{T}BU dosing, in which BU doses were personalized using therapeutic drug monitoring to ensure that patients achieved the intended BU plasma AUC [7]. Therefore, BU itself did not likely contribute to the different clinical outcomes between ^{T}BU/CY and CY/^{T}BU in the trial reported by Rezvani et al [4].

In addition to phenytoin administration before CY (ie, BU/CY) increasing 4HCY AUC, BU administration depletes hepatic glutathione, thereby sensitizing the liver to toxic effects of CY and its metabolites [4,8,9]. In patients with myelofibrosis, the CY/^{T}BU regimen was associated with less sinusoidal obstruction syndrome during the first 20 days post-HCT, a statistically significant lower risk of nonrelapse mortality (NRM) during the first 100 days post-HCT, but no statistically significant differences in NRM or overall survival at 2 years post-HCT [4]. In contrast, in patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS), the CY/^{T}BU regimen was associated with a statistically significantly greater risk of relapse after HCT; the cumulative incidence was 44% for patients treated with CY/^{T}BU versus 20% for those treated with ^{T}BU/CY. The unadjusted hazard ratio (HR) was 2.57 (P = .008), and the adjusted HR was 2.15 (P = .02). This observation in the CY/^{T}BU regimen raises concern that relapse rates may be higher when alternative AEMs are administered in patients with AML or MDS, because unlike phenytoin, they do not increase 4HCY AUC, and intracellular concentrations of the active CY metabolites may be lower in patients treated with alternative AEMs compared with those treated with phenytoin.

In addition to its effect on CY metabolism, phenytoin increases the clearance of orally administered BU [10]. The effect of phenytoin on i.v. BU clearance is less clear. The available studies have shown either a slight effect [11] or no measurable effect [12-14] on i.v. BU clearance. Therefore, in the absence of targeted BU dosing, replacing phenytoin with an alternative AEM would be expected to increase BU AUC after oral BU administration, but not after i.v. BU administration. When comparing ^{T}BU/CY and CY/^{T}BU regimens, Rezvani et al [4] used targeted BU dosing to ensure consistent BU AUCs.

Patients treated with BU/CY differ from those treated with CY/BU in another potentially important respect. As discussed above, depletion of glutathione during BU administration may sensitize the liver to toxicity after subsequent exposure to CY and its metabolites [8]. Therefore, it is difficult to predict whether the use of alternative AEMs and the associated lower intracellular concentrations of active CY metabolites would affect NRM and regimen-related toxicity. Nonetheless, the results reported by Rezvani et al [4]. raise concerns that the use of alternative AEMs may be associated with a greater risk of relapse after HCT in patients treated with BU/CY conditioning regimens.

Many HCT centers have already adopted the use of alternative AEMs to prevent BU-induced seizures. Although alternative AEMs are effective for this indication [1], previous reports with <50 cases have not been powered sufficiently to evaluate whether relapse, NRM, or overall survival might be affected by the use of alternative AEMs compared with phenytoin in patients treated with BU/CY conditioning regimens [1,3,15-17]. Therefore, we conducted a large retrospective study using the Center for International Blood and Marrow Transplant Research (CIBMTR) registry data to compare longer-term outcomes associated with the use of alternative AEMs and the use of phenytoin in patients treated with a BU/CY conditioning regimen before allogeneic HCT.

METHODS

Data Source

The CIBMTR is a working group of more than 500 transplantation centers worldwide that contribute detailed data on HCT to a statistical center at the Medical College of Wisconsin. The CIBMTR is a research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin. Participating centers are required to report all transplantations consecutively; patients are followed longitudinally, and compliance is monitored by onsite audits. Data quality is ensured both by computerized checks for discrepancies and by physicians' review of submitted data. The CIBMTR conducts observational studies and complies with all applicable federal regulations that protect human subjects.

Patient Selection

The study cohort included patients who underwent a first allogeneic HCT after BU and CY conditioning with a graft from an HLA-matched sibling or an unrelated donor at a US center during calendar years 2004 through 2014. Patients were excluded who had a seizure disorder before HCT, had not provided consent, had undergone HCT at a center that failed data audits, or if did not report post HCT follow-up data. Patients were also excluded who had undergone HCT for treatment of myelofibrosis in the absence of another hematologic malignancy, severe aplastic anemia or other nonmalignant disease; had received total body irradiation or an antineoplastic medication other than BU and CY in the conditioning regimen before HCT or CY for immunosuppression after HCT; had received CY before BU; or had missing dates of CY or BU administration. This screen identified 2863 patients from 153 centers who were potentially eligible for the study.

CIBMTR case report forms do not collect information regarding AEMs used to prevent BU-induced seizures. Therefore, HCT centers were invited to participate in the study by completing a survey describing center-specific practices regarding the use of phenytoin versus alternative AEMs, including the dates of any changes in practice and differences in practices between children and adults. Ninety-two centers returned information (Supplementary

Table 1), and an additional data review excluded patients who received BU at a total dose <8 mg/kg or CY at a total dose <100 mg/kg from a participating center. The final cohort included 2155 patients, of whom 1460 received phenytoin and 695 received alternative AEMs.

Study Objectives and Definitions

The overall study objective was to evaluate outcomes after the use of alternative AEMs (ie, any AEM other than phenytoin or fosphenytoin) compared with the use of phenytoin (ie, phenytoin or fosphenytoin). The efficacy of these AEMs—that is, how well they prevented BU-induced seizures—could not be assessed, because the CIBMTR repository does not collect data on seizures after BU administration. The primary question to be addressed was whether the use of alternative AEMs is associated with a higher risk of recurrent or progressive malignancy (ie, relapse). Other endpoints included overall survival, survival without recurrent or progressive malignancy (ie, disease-free survival), NRM (ie, death without previous recurrent or progressive malignancy), grade II-IV acute graft-versus-host disease (GVHD), grade III-IV acute GVHD, chronic GVHD, renal failure requiring dialysis, idiopathic pneumonia syndrome, and sinusoidal obstruction syndrome, all as reported in CIBMTR case report forms [18,19].

Statistical Analysis

For analysis of the main effect, the patients were categorized into 1 of 2 groups based on the AEM used, either phenytoin (ie, phenytoin or fosphenytoin) or alternative AEMs. Multivariable analysis used a Cox proportional hazards model for each endpoint. Candidate variables considered in these analyses are listed in Supplementary Table 2. All variables were first tested for affirmation of the proportional hazards assumption. Factors violating the proportional hazards assumption were adjusted through stratification. Then a stepwise forward-backward procedure was performed to select the adjusted clinical variables and to build the multivariable models, using a .05 threshold of statistical significance for both inclusion and exclusion in the model. Interactions between the main variable AEM group (ie, phenytoin versus alternative AEM) and the selected adjusted covariates were tested in each model, and no endpoint showed any covariate interactions at a .01 threshold of statistical significance. The center effect was adjusted in all multivariable models through robust sandwich estimates. All P values are 2-sided. To account for multiple testing, α = .01 was chosen as the significance level for the impact of AEM group on outcomes. Cumulative incidence frequencies and HRs were used to evaluate relapse in the 2 AEM groups. Because malignancies may differ in their susceptibility to CY and its metabolites, a subset analysis compared the risk of relapse between the 2 AEM groups separately in patients with AML, chronic myelogenous leukemia (CML), MDS, or a lymphoid malignancy. A similar analysis compared the risks of relapse between the 2 AEM groups in adults (age ≥18 years) and children (age <18 years). Data analyses were performed using SAS version 9.4 (SAS I nstitute, Cary, NC).

Noninferiority of the alternative AEM group for the key endpoint of relapse was assessed by comparing the upper limit of the 95% CI of the HR to a prespecified noninferiority margin of 1.21, corresponding to an absolute difference in risk of relapse of approximately 5% at 2 years. Assuming that the alternative AEM group versus the phenytoin groups has an HR of 1.21 for relapse, and given a 30% incidence of relapse at 2 years in the phenytoin group, with 2150 patients distributed at a 2:1 ratio between the phenytoin and alternative AEM groups, our analysis had 83% and 63% power to detect the difference based on the log-rank test at .05 and .01 significance, respectively.

RESULTS

Patient and Treatment Characteristics

The median age of patients within each AEM group was similar at 46 years for the phenytoin group and 47 years for the alternative AEM group (Table 1). Most patients were adults (age ≥18 years), comprising 90% of those in the phenytoin group and 82% in the alternative AEM group. Ursodiol prophylaxis was administered to 6% of the patients in each group. More than one-half of the patients had AML, and more than two-thirds received an unrelated donor graft. Most patients were treated with i.v. BU, including 77% of patients in the phenytoin group and in 92% of those in the alternative AEM group. Supplementary Table 3 summarizes characteristics of patients subdivided according to BU administration route. BU therapeutic drug monitoring and personalized dose adjustments were used in 21% of patients in the phenytoin group and in 52% of those in the alternative AEM group, but detailed BU pharmacokinetic data are not available. Thus, the impact of AEMs on BU pharmacokinetics in this cohort cannot be evaluated. Approximately two-thirds of the patients received growth factor-mobilized blood cell grafts, and <10% received cord blood grafts. Most patients received a calcineurin inhibitor with methotrexate for immunosuppression after HCT. In both children and adults, the use of alternative AEMs gradually increased between 2004 and 2011 (Figure 1). The proportion of children treated with alternative AEMs increased sharply in 2012, but the proportion of adults treated with alternative AEMs did not (Figure 1).

Table 1
Patient characteristics

Variable	Phenytoin	Alternative AEM
Number of patients	1460	695
Number of centers	72	59
Patient age, yr, median (range)	46 (<1-70)	47 (<1-71)
Patient age, yr, n (%)		
≥18	1310 (90)	572 (82)
<18	150 (10)	123 (18)
Male sex, n (%)	781 (53)	354 (51)
Disease, n (%)		
AML	799 (55)	471 (68)
MDS	318 (22)	126 (18)
CML	212 (15)	63 (9)
NHL	47 (3)	7 (1)
ALL	39 (3)	12 (2)
Other*	45 (3)	16 (3)
Donor type, n (%)		
HLA-identical sibling	498 (34)	237 (34)
Unrelated or umbilical cord blood	962 (66)	458 (66)
Graft type, n (%)		
Growth factor-mobilized blood	950 (65)	481 (69)
Bone marrow	445 (30)	158 (23)
Umbilical cord blood	65 (4)	56 (8)
BU administration route, n (%)†		
i.v.	1130 (77)	637 (92)
Oral	318 (22)	57 (8)
BU cumulative dose, mg/kg, median (range)‡	13 (8-37)	13 (8-26)
BU pharmacokinetics obtained, n (%)		
Missing	740 (51)	164 (24)
No	414 (28)	173 (25)
Yes	306 (21)	358 (52)
CY cumulative dose, mg/kg, median (range)	120 (100-247)	120 (101-278)
CY dose, mg/kg, n (%)		
100-130	1252 (86)	576 (83)
131-170	59 (4)	22 (3)
171-186	16 (1)	3 (<1)
187-278	133 (9)	94 (14)
Follow-up of survivors mo, median (range)	73 (3-139)	61 (3-123)

NHL indicates non-Hodgkin lymphoma; ALL, acute lymphoblastic leukemia.
* Hodgkin disease, myeloproliferative syndrome, myeloma, and other leukemias.
† Information regarding BU administration route was not available for 12 patients in the phenytoin group and 1 patient in the alternative AEM group.
‡ BU doses >8 mg/kg (either oral or i.v.) were used.

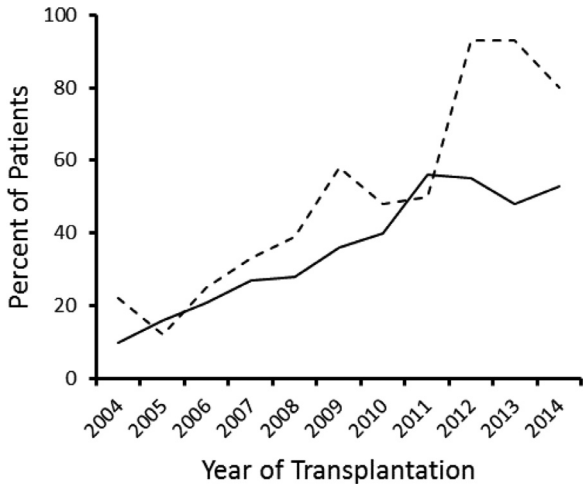

Figure 1. Use of alternative AEMs to prevent BU-induced seizures increased between 2004 and 2014. Plots show the percentages of adult (solid line) and pediatric (dashed line) patients treated with alternative AEMs according to year of HCT.

Outcomes in the Different AEM Groups

The median follow-up of patients after HCT was 73 months (range, 3-to 139 months) in the phenytoin group and 61 months (range, 3 to 1233 months) in the alternative AEM group. i.v. BU use differed between the two AEM groups: 78% in the phenytoin group and 92% in the alternative AEM group ($P < .0001$). Thus, for each AEM group, outcomes with i.v. BU were compared with outcomes with oral BU (Supplementary Table 4). None of the outcomes differed between the 2 AEM groups at the significance threshold of $P = .01$. With the less stringent criteria ($P < .05$), in the phenytoin group, grade II-IV acute GVHD and idiopathic pneumonia syndrome were less likely with i.v. BU compared with oral BU. In the alternative AEM group, NRM and grade III-IV acute GVHD were more likely with i.v. BU compared with oral BU. Therefore, the analysis of AEM groups was stratified according to BU administration route.

Figure 2 shows the results of analyses incorporating covariate information from all patients in a single model. Among the patients treated with i.v. BU for whom dialysis data were available, the risk of dialysis was lower in the alternative AEM group than in the phenytoin group (HR, .52; 95% CI, .34 to .79; $P = .003$). Among the patients included in the model, dialysis was required in 29 of 608 (4%) in the alternative AEM group and in 70 of 1073 (7%) in the phenytoin group. The .49 HR point estimate for the risk of dialysis among patients treated with oral BU approximates the .52 HR point estimate among patients treated with i.v. BU. No other outcome showed a difference between the 2 groups at a .01 threshold of statistical significance.

Among patients treated with oral BU, the risks of grade II-IV GVHD and sinusoidal obstruction syndrome were lower in the alternative AEM group compared with the phenytoin group (HR, .57; 95% CI, .38 to .86; $P = .01$ versus HR, .24; 95% CI, .08 to .71; $P = .01$). Among patients in the model, grade II-IV GVHD occurred in 22 of 56 patients (39%) in the alternative AEM group, compared with 182 of 317 (57%) in the phenytoin group, and sinusoidal obstruction syndrome was reported in 1 of 57 patients (2%) in the alternative AEM group, compared with 25 of 318 (8%) in the phenytoin group. The HR point estimates for these associations were considerably lower among patients treated with oral BU compared with patients treated with i.v. BU. Other outcomes showed no statistically significant differences between the 2 AEM groups.

The adjusted HR for relapse in the alternative AEM group compared with the phenytoin group in the entire cohort of 2155 patients was 1.04 (95% CI, .89 to 1.23; $P = .60$). The upper limit of the 95% confidence interval is slightly higher than the noninferiority limit of 1.21 prespecified by the protocol. The risk of relapse did not differ between AEM groups when patients were stratified according to pretransplantation disease (AML, CML, MDS, or lymphoid malignancy) (Figure 3). The adjusted HR of relapse in the alternative AEM group compared with the phenytoin group was .96 (95% CI, .80 to 1.15; $P = .63$) among all adult patients and 1.61 (95% CI, 1.00 to 2.61; $P = .05$) among all pediatric patients (Figure 4).

Outcomes in Adults and Children

To determine whether results differed between children and adults, we compared outcomes in the phenytoin and alternative AEM groups in pediatric and adult patients who received i.v. BU for treatment of AML, CML, MDS, or lymphoid malignancies. The number of children who received oral BU was too small to allow for an informative comparison with adults who received oral BU. As shown in Figure 5, results comparing the phenytoin and alternative AEM groups in adults who received i.v. BU did not differ from those shown in Figure 2, as expected from the preponderance of adults in the overall cohort. In pediatric patients treated with i.v. BU, the risk of interstitial pneumonia syndrome was greater in the alternative AEM group than in the phenytoin group (adjusted HR, 3.10; 95% CI, 1.26 to 7.64; $P = .01$). In addition, the risk of relapse appeared to be higher in the alternative AEM group compared with the phenytoin group (adjusted HR, 1.61; 95% CI, 1.00 to 2.61; $P = .05$) (Figure 5). Doses of BU and CY did not differ between pediatric patients in the alternative AEM group compared with the phenytoin group (data not shown). A statistical interaction test did not show a difference in the HR of relapse between adults and children treated with i.v. BU ($P = .11$), but the small number of pediatric patients treated with i.v. BU (n = 252) should be noted.

DISCUSSION

The results of this large (n = 2155) retrospective study support 3 main conclusions in patients conditioned for allogeneic HCT with BU/CY: (1) AEMs other than phenytoin are safe for use to prevent BU-induced seizures; (2) the use of alternative AEMs does not adversely affect the risk of relapse, and (3) the risk of renal failure requiring dialysis is lower in adults receiving i.v. BU when alternative AEMs are used instead of phenytoin.

Seizures have been reported at frequencies ranging from 2% to 40% in patients receiving BU without the use of an AEM to prevent this complication [20-23]. BU freely crosses the blood-brain barrier, and BU concentrations in the central nervous system are similar to plasma concentrations, which most likely accounts for the neurotoxicity associated with BU [22,24]. BU-induced seizures are typically generalized tonic-clonic in character and usually occur within the period between the second day of BU administration and the first 24 hours after the last BU dose [1]. Therefore, prophylaxis for BU-induced seizures should begin before starting treatment with BU and should be continued throughout BU administration.

Characteristics of the ideal BU-induced seizure prophylaxis include lack of overlapping toxicity with the conditioning regimen, lack of interference with engraftment of donor cells, and

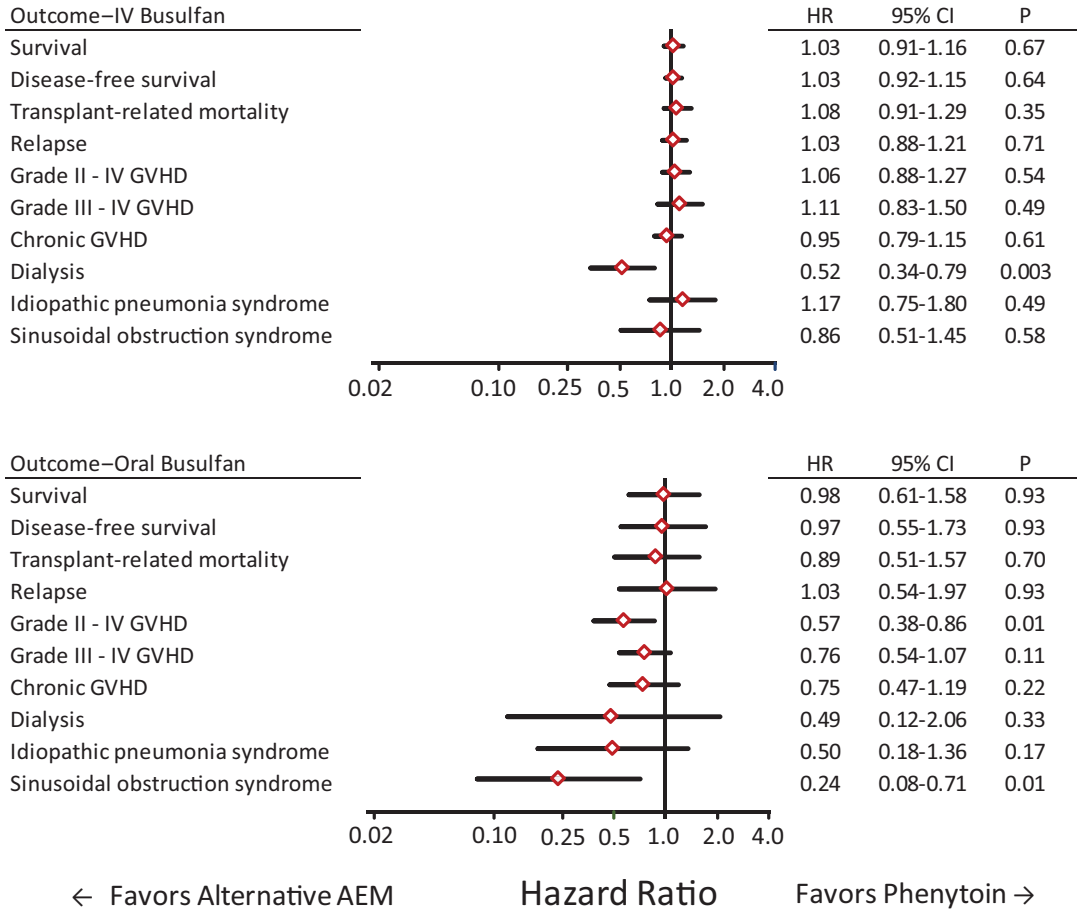

Figure 2. Most outcomes did not differ between patients who received alternative AEMs and those who received phenytoin after conditioning with oral or i.v. BU followed by CY. Diamonds indicate the HR point estimates comparing results for the alternative AEM group and phenytoin group. Bars indicate the 95% CIs. Each statistical model includes risk factor covariate adjustments derived from the entire cohort.

minimal potential for pharmacokinetic drug interactions [1]. Given these criteria, phenytoin suffers from possible toxicities and is especially ill-suited because of drug interactions. The standard of care for prevention of seizures in patients with generalized tonic-clonic seizure disorders shifted from phenytoin to alternative AEMs after their approval by the Food and Drug Administration in the 1990s [25,26]. Acceptance of alternative AEMs to prevent BU-induced seizures in HCT recipients has been slow; as of 2014, phenytoin was still used in approximately 50% of adults at centers providing data for the present study (Figure 1).

The lower incidence of dialysis associated with the use of alternative AEMs instead of phenytoin in adults could reflect the absence of CYP3A induction. CYP3A is induced by phenytoin and may increase dechlorocyclophosphamide and chloroacetaldehyde formation in the kidneys (Supplementary Figure 1). Chloroacetaldehyde has concentration-dependent cytotoxic effects on cultured porcine and rabbit renal tubules and on isolated perfused rat kidneys [27-29]. The use of alternative AEMs was not associated with a lower incidence of dialysis in children; however, the use of alternative AEMs appeared to be associated with a higher risk of idiopathic pneumonia

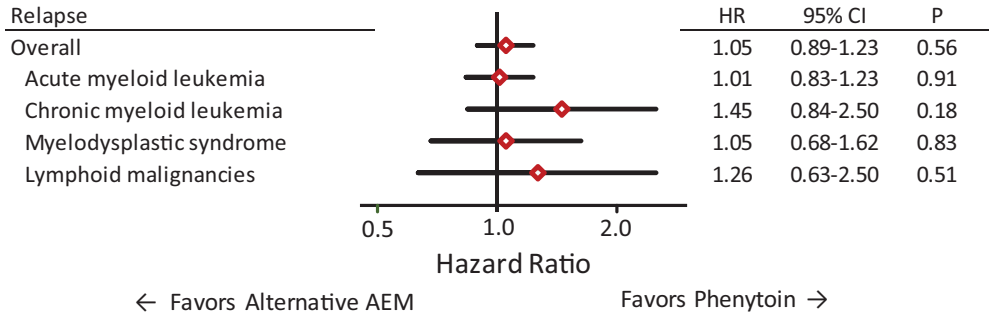

Figure 3. The risk of relapse did not differ between patients who received alternative AEMs and those who received phenytoin after conditioning with BU followed by CY for treatment of AML, CML, MDS, or a lymphoid malignancy. Diamonds indicate the HR point estimates of relapse for the alternative AEM group compared with the phenytoin group. Bars indicate the 95% CIs. Each statistical model included risk factor covariate adjustments derived from the entire cohort.

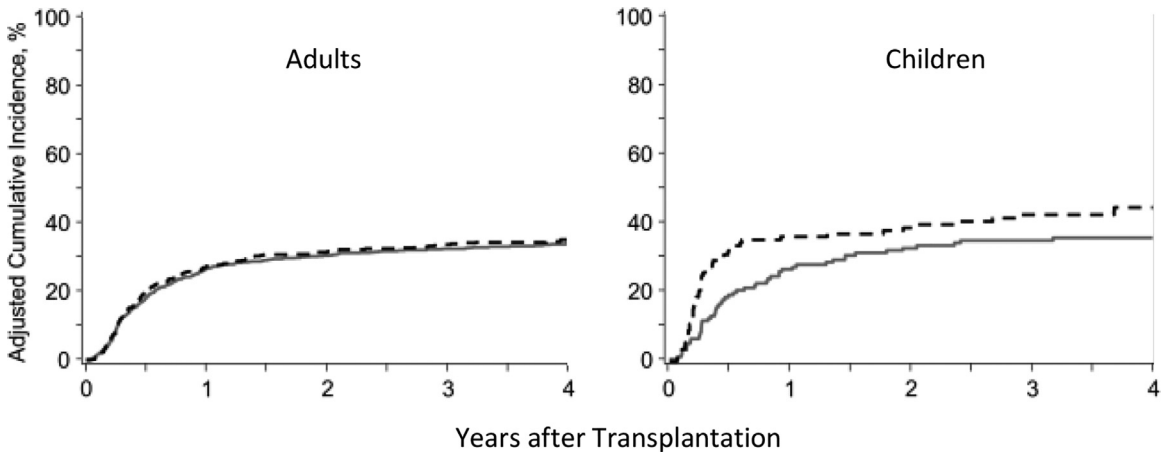

Figure 4. In adult and pediatric patients, the adjusted cumulative incidence of relapse did not differ between those who received phenytoin (solid lines) and those who received alternative AEMs (dashed lines) after conditioning with BU followed by CY. In pediatric patients, the risk of relapse appeared to differ between the AEM groups, but the *P* value of .05 did not meet the .01 threshold of statistical significance for this study (see Methods).

syndrome in children but not in adults (Figure 5). The reasons for these possible age-related differences between adults and children are not apparent.

Interest has emerged in developing novel high-dose conditioning regimens that replace CY with fludarabine (FLU), a purine nucleoside inhibitor that is potentially less toxic yet has similar immunosuppressive and antileukemic efficacy as CY [30,31]. Our present results do not apply to patients receiving BU in combination with FLU [30,31], because the drug-metabolizing enzymes and transporters of CY and FLU differ, such that

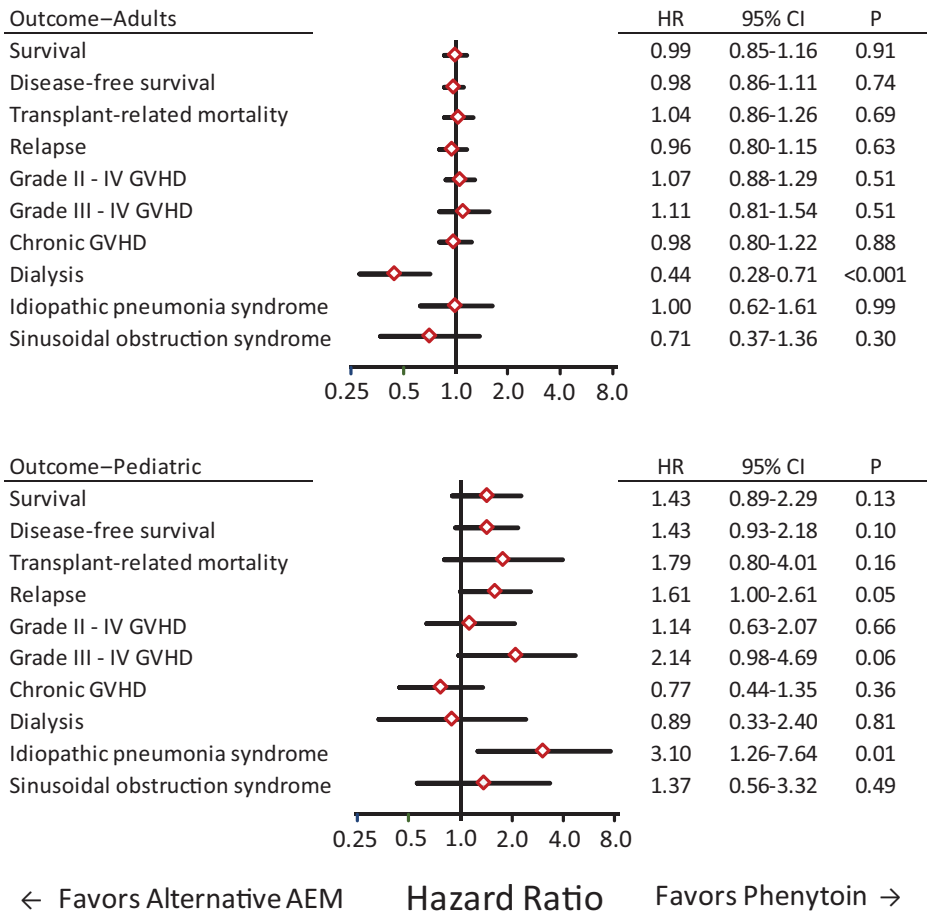

Figure 5. Most outcomes did not differ between patients who received alternative AEMs and those who received phenytoin in adult (top) and pediatric (bottom) patients after conditioning with i.v. BU followed by CY for treatment of AML, CML, MDS, or lymphoid malignancy. Diamonds indicate the HR point estimates for outcomes comparing results for the alternative AEM group and the phenytoin group. Bars indicate the 95% CIs. Each statistical model included risk factor covariate adjustments derived from the entire cohort. The number of pediatric patients who received oral BU is too small to allow for an informative comparison with adult patients who received oral BU.

phenytoin would not be expected to affect the pharmacokinetics of FLU or its metabolites. Administration of CY before BU (CY/BU), as was done by Rezvani et al [4], is another approach to making the regimen more tolerable. Our present results do not apply to patients receiving CY/BU because of this regimen's different antileukemic efficacy and toxicity compared with BU/CY [4]. We did not expect to find higher rates grade II–IV acute GVHD or idiopathic pneumonia syndrome with the use of i.v. BU compared with oral BU within the phenytoin group. Several other retrospective analyses have compared outcomes between oral and i.v. BU [32-38], but results have been difficult to interpret because of heterogeneity among patient cohorts and insufficient details regarding the AEM, BU dose, or BU pharmacokinetics.

This study has some limitations. We could not compare the efficacy of seizure prophylaxis in the 2 AEM groups because the CIBMTR repository does not collect data regarding seizures after BU administration. Case series have reported the effectiveness of these alternative AEMs [17], as reviewed previously [1]. Supplementary Table 5 provides a practical reference of some of the commonly used AEMs to prevent BU-induced seizures. Our results might not reflect actual AEM use across all HCT centers, because not all centers provided data, and patterns of use at centers that provided data might not be representative of those at other centers. Furthermore, detailed information (eg, drug name, dose) about the alternative AEMs used was not collected. Thus, we cannot recommend a specific alternative AEM.

Finally, some variables that could affect clinical outcomes were not available. For example, the risk of sinusoidal obstructive syndrome is inversely correlated with the interval from the last BU dose to the first CY dose [39], and variation in the use of therapeutic drug monitoring, personalized BU dosing, and target BU AUC could affect outcomes [7], although we have no reason to suspect that these practices differed between the AEM groups. Future CIBMTR registry studies would benefit from the collection of such information [40]. A much larger pediatric cohort with information on BU dose, administration frequency, and plasma AUC is needed to determine whether the use of alternative AEMs is associated with an increased risk of relapse (Figure 4).

It should be noted that a statistical interaction test did not show a differing HR of relapse between adults and children treated with i.v. BU ($P = .11$), although only 273 children (accrued over 10 years) received BU/CY (Table 1). A study designed to address the observed difference between a .25 incidence of relapse at 1 year with phenytoin versus a .35 incidence with alternative AEMs at .8 power and a 2-sided .05 type 1 error with a 1:1 allocation between arms would require approximately 650 patients. At the historical enrollment rate of 27 pediatric patients per year, it would take approximately 24 years to conduct such a study, which clearly is infeasible.

To mitigate concerns about relapse with alternative AEM in BU/CY-conditioned children, consideration could be given for replacing CY. For example, fludarabine could replace CY, given that phenytoin would not be expected to affect the pharmacokinetics of FLU or its metabolites.

Although this study had limited power to exclude adverse outcomes associated with the use of alternative AEMs in evaluating low-frequency events and in analyzing subgroups of patients, the power was sufficient to ensure that any differences in the risk of relapse are smaller than might have been expected from the results reported by Rezvani et al [4]. We speculate that differences in 4HCY AUC between the alternative and phenytoin AEM groups had very little effect on malignant and normal hematopoietic stem cells, because the high aldehyde dehydrogenase activity in these cells diverted 4HCY disposition toward CEPM and away from phosphoramide mustard, thereby protecting them from DNA cross-linking and toxicity.

In conclusion, we found no statistically significant evidence suggesting worse outcomes with the use of alternative AEMs compared with phenytoin to prevent BU-induced seizures in patients treated with BU/CY conditioning regimens before allogenic HCT. Our data show no meaningful differences in the available safety outcomes between the 2 AEM treatment groups. Given the undesirable toxicities and drug interactions caused by phenytoin, the use of alternative AEMs is justified to prevent BU-induced seizures, and the use of phenytoin may be limited to a backup option.

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*Corporate member.

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SUPPLEMENTARY DATA

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