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Prior Gemtuzumab Ozogamicin Exposure in Adults With Acute Myeloid Leukemia Does Not Increase Hepatic Veno-occlusive Disease Risk After Allogeneic Hematopoietic Cell Transplantation: a CIBMTR Analysis

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Abstract

Gemtuzumab ozogamicin (GO) therapy prior to allogeneic hematopoietic cell transplantation (alloHCT) has been historically associated with an increased risk of hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) in patients with acute myeloid leukemia (AML). The current analysis examined VOD/SOS risk and outcomes in a cohort of patients who in recent years reported to the Center for International Blood & Marrow Transplant Research. Adults with AML who had GO exposure prior to myeloablative alloHCT were matched 1:4 by age and disease status at transplant to recipients without GO exposure (controls). A total of 137 patients with GO exposure and 548 matched controls who underwent alloHCT between 2008 and 2011 were included in this analysis. With a median ~8-year follow-up of survivors, the 5-year overall survival probability was similar in the 2 cohorts: 38% and 38% in the GO-exposed versus control (P = .97) group. Incidence of VOD/SOS and severe VOD/SOS, respectively, at 100 days

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Declaration of Interest

VTH has served as a consultant for Jazz Pharmaceuticals. ASM, WSP, PS, M-JZ, and WS: none. DC was an employee of Pfizer at the time of manuscript development. CJH and FRL are employees of and have equity ownership in Pfizer.

Data Statement

CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. These policies hold that data that correspond to and support publications should be made as widely and freely available as possible while safeguarding the privacy of participants and protecting confidential and proprietary data. As of January 1, 2020, and in accordance with journal embargo policy, CIBMTR will make available on its public website de-identified analysis datasets and corresponding data dictionaries.

was 4% (95% confidence interval [CI]: 1–7) and 3% (95% CI: 1–6) in GO-exposed patients and 3% (95% CI: 2–5) and 1% (95% CI: 0–2) in controls. Correspondingly, among patients who developed VOD/SOS, 1-year survival probability after VOD/SOS diagnosis was 33% (95% CI: 5–72) and 27% (95% CI: 11–47) ($P = .78$). In multivariate analyses, GO exposure prior to alloHCT was not associated with an increased risk of VOD/SOS (odds ratio 1.10; $P = .85$) or death (hazard ratio 1.08; $P = .57$). Three (3%) deaths in the GO group and 3 (<1%) deaths in the control group were attributed to VOD/SOS. Our results suggest that GO treatment prior to myeloablative alloHCT in the recent era is not associated with an increased risk of post-transplant VOD/SOS or death.

INTRODUCTION

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication that occurs primarily after hematopoietic cell transplantation (HCT) [1]. VOD/SOS is characterized by fluid retention, painful hepatomegaly, weight gain, and hyperbilirubinemia and results from injury to the sinusoidal endothelial cells due, at least in part, to the conditioning regimen [1,2]. The rate of VOD/SOS following HCT in historical cohorts ranges from 0 to 62.3%, with a mean of 13.7%, and is higher with allogeneic HCT (alloHCT) compared with autologous HCT [3]. However, the incidence of VOD/SOS following alloHCT is decreasing as a result of advances in supportive care, improved understanding of risk factors, and increased use of less toxic and reduced-intensity conditioning regimens [4–6].

VOD/SOS occurs primarily in the context of HCT, but is also associated with exposure to certain chemotherapeutic agents, such as gemtuzumab ozogamicin (GO) [3,7–9]. GO is an antibody drug conjugate composed of the CD33-directed monoclonal antibody covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. The CD33 antigen is expressed on leukemic blasts in the vast majority of patients with acute myeloid leukemia (AML) and is an important target for antibody-based AML therapies [10]. VOD/SOS has been reported in patients exposed to GO, with and without alloHCT [7]. Treatment with GO prior to alloHCT may place patients at an increased risk of developing VOD/SOS post transplant [11]. In a pooled analysis of 9 clinical trials, the rate of post-transplant VOD/SOS was 37%, with a range of 20 to 89%, among patients treated with GO prior to alloHCT [8].

Fractionated dosing of GO has been examined as a strategy for reducing hepatotoxicity while maintaining the efficacy of GO for AML treatment. The pivotal phase 3 ALFA-0701 trial examined efficacy and safety of adding fractionated, low-dose GO (3 mg/m^2 on days 1, 4, and 7 of induction and day 1 of consolidation) to standard chemotherapy versus standard chemotherapy alone. Results of this trial demonstrated improved outcomes with the addition of GO; a low rate of VOD/SOS was also observed, including in patients who proceeded to HCT [12–14].· Based on ALFA-0701 and other key clinical trials, GO was re-approved in the United States (US) in 2017 for the treatment of adults with newly diagnosed CD33-positive (CD33+) AML and adults and children (aged ≥2 years) with relapsed/refractory CD33+ AML [7].

In this registry analysis, we examined VOD/SOS risk and outcomes in a recent cohort of adults with AML who received myeloablative alloHCT with and without prior GO exposure and reported to the Center for International Blood & Marrow Transplant Research (CIBMTR) database. As this cohort received alloHCT prior to the 2017 re-approval of GO by the US Food and Drug Administration (FDA), patients were administered GO based on the original FDA approval, which had a higher recommended dose and no fractionated dosing schedule [15]. However, our primary objective was to examine VOD/SOS risk after myeloablative alloHCT in GO-exposed patients in recent years, regardless of GO dosage and administration schedule.

METHODS

Patients and Study Design

The CIBMTR is a research collaboration between the Medical College of Wisconsin in Milwaukee, WI, and the National Marrow Donor Program® / Be The Match® (Minneapolis, MN; www.CIBMTR.org). CIBMTR operates a large outcomes database in HCT and, recently, non-HCT cellular therapies for diverse indications. The CIBMTR relies on the collaboration of more than 420 centers worldwide that share data on treated patients. The CIBMTR has data for more than 495,000 transplant recipients and receives data for more than 24,000 new transplants each year.

This retrospective, matched-cohort analysis included adult patients with AML who underwent first myeloablative alloHCT with versus without prior GO exposure between 2008 and 2011 and reported to the CIBMTR at the Comprehensive Report Form (CRF) level. Patients were randomly selected through a weighted randomization scheme for the CRF level of data collection, which captures detailed patient-, disease-, and transplant-related data further to the standard data collection. All data were collected pre-transplant, 100 days and 6 months post-transplant, annually until 6 years post-transplant, and biannually thereafter until death.

Adults with GO exposure before first myeloablative alloHCT were matched 1:4 to patients without GO exposure (controls) by age and disease status (complete remission [CR]1, CR≥2, and relapse/primary induction failure) at alloHCT. Matching was an iterative process whereby each case was matched to a pool of possible controls on disease status and age within 5 years, and the control with the smallest age difference was selected. This process was performed for each case, after which the process was repeated to add additional controls. The matching process was complete after each GO-exposed patient was matched to 4 controls.

Due to the small number of VOD/SOS events in the reduced-conditioning cohort and the expected differences in outcomes between myeloablative and non-myeloablative/reduced-intensity conditioning, the study population was limited to those who received myeloablative conditioning (Supplementary Table S1). The cutoff year 2011 was chosen because few GO-exposed patients in the database received alloHCT after 2011, as GO was withdrawn from the market the prior year. Patients who did not consent to research, patients whose data were embargoed from research studies, and syngeneic twins were also excluded from the analysis.

Outcomes

The primary outcome was the incidence of VOD/SOS at 100 days following alloHCT. Secondary outcomes were overall survival (OS) rates at 100 days, 6 months, and 1, 3, and 5 years, disease-free survival (DFS), relapse, and nonrelapse mortality (NRM) rates at 1, 3, and 5 years, and graft-versus-host disease (GVHD).

Diagnosis of VOD/SOS

VOD/SOS was diagnosed using the Modified Seattle criteria, the Baltimore criteria, autopsy/biopsy, or other criteria as reported by the individual centers. The Modified Seattle criteria requires ≥2 of the following within 20 days of alloHCT: serum bilirubin >34 umol/L (>2 mg/dL), hepatomegaly with right upper quadrant pain, and 2% weight gain from baseline due to fluid retention [16]. The Baltimore criteria requires serum bilirubin >34umol/L (>2 mg/dL) within 21 days of alloHCT and ≥2 of the following: hepatomegaly, 5% weight gain from baseline, and ascites [2]. Other diagnostic criteria included various combinations of ascites, serum bilirubin >2.0 mg, elevated liver enzymes, abnormal ultrasonography, hepatomegaly, and weight gain. Severe VOD/SOS was defined as VOD/SOS associated with renal impairment requiring dialysis or any noninfectious pulmonary abnormality.

Statistical Analyses

The cumulative incidences of VOD/SOS and severe VOD/SOS at 100 days were calculated using the cumulative incidence estimator to accommodate competing risks. Death without development of VOD/SOS was considered a competing risk. Probabilities of OS and DFS were calculated using the Kaplan–Meier method, and probabilities of relapse and NRM were calculated using the cumulative incidence estimator.

Multivariate analysis was performed for VOD/SOS at 100 days, OS, DFS, relapse, and NRM. To accommodate matched pairs, marginal logistic regression models were used to compare the incidence of VOD/SOS at day 100 between GO-exposed patients and controls, and marginal Cox regression models were used to examine the effect of GO exposure on OS, DFS, relapse, and NRM. Variables considered for adjustment in the models were recipient age, recipient sex, Karnofsky performance score, HCT-comorbidity index (HCT-CI), cytogenetics, disease status at alloHCT, conditioning regimen, pharmacokinetics for busulfan, donor type, cytomegalovirus match, graft type, GVHD prophylaxis, sirolimus usage, antithymocyte globulin/alemtuzumab usage, and hepatitis B and C status (Supplementary Table S2). All factors that attained a $P \leq .05$ were held in the final model with the exception of GO exposure, which was held in all steps of the model building regardless of level of significance.

RESULTS

Patients and Treatment

A total of 137 patients with GO exposure and 548 patients without GO exposure (controls) prior to myeloablative alloHCT were included in the analysis (Table 1). Median (range) age at transplant was 42 (18–73) years for GO-exposed patients and 38 (18–74) years for controls. In both arms, 33% of patients were in CR1, 30% in CR≥2, and 37% in relapse or

primary induction failure prior to alloHCT; a majority of patients had a Karnofsky performance score ≥90. All patients received myeloablative conditioning: 56 (41%) patients with GO exposure and 140 (45%) controls received a regimen containing total body irradiation and 81 (59%) and 168 (55%) received a regimen with chemotherapy only. Cyclophosphamide was included in the conditioning regimen of 82 (60%) patients with GO exposure and 378 (69%) controls. In all, 10 (7%) patients with GO exposure and 23 (4%) controls received prophylactic ursodeoxycholic acid; no patient in either arm received prophylactic defibrotide.

Among patients with GO exposure, median (range) time from last GO exposure to transplant was 4 (2–10) months for patients in CR1 prior to alloHCT, 7 (1–52) months for patients in CR≥2, and 3 (<1–76) months for patients in relapse/primary induction failure.

GO dosing data were obtained for 58 (42%) of the 137 patients with GO exposure. All patient-, disease-, and transplant-related characteristics were balanced between patients with versus without dosing data (Supplementary Table S3). Therefore, the subset of patients with supplemental dose data can be considered representative of all GO-exposed patients in this analysis.

Among patients with available dosing data, median (range) total GO dose was 9.5 (3.0–33.0) mg. All 58 patients received GO in combination with chemotherapy. Characteristics were generally balanced between patients who received <10 versus ≥10 mg total GO, although patients receiving <10 mg were more likely to have poor cytogenetics (43% vs. 21%) and to be in CR1 at transplant (40% vs. 29%; Table 2). Fractionated-dose GO was administered in 8 (27%) patients receiving <10 mg total dose and in 11 (39%) patients who received ≥10 mg total dose. The corresponding median (range) number of cycles of GO prior to alloHCT was 1 (1–3) versus 1 (1–3) and median (range) time from last GO dose to transplant 4 (1–12) versus 3 (1–15) months.

Incidence of VOD/SOS

The cumulative incidence (95% confidence interval [CI]) of VOD/SOS and severe VOD/SOS, respectively, at 100 days was 4% (1–7%) and 3% (2–5%) in patients with GO exposure and 3% (1–6%) and 1% (0–2%) in controls (Table 3). In patients who received cyclophosphamide as part of the conditioning regimen, the cumulative incidence (95% CI) of VOD/SOS at 100 days was 2% (0–7%) and 2% (1–4%) in the GO and control arms, respectively.

Six patients with GO exposure developed VOD/SOS; diagnosis was ascertained by autopsy/biopsy (n = 1), Baltimore criteria (n = 1), and other clinical diagnostic criteria (n = 4). Median (range) time from last GO dose to alloHCT among these 6 patients was 3 (2–5) months. A total of 22 controls developed VOD/SOS; diagnosis was ascertained by autopsy/biopsy (n = 8), Baltimore criteria (n = 2), modified Seattle criteria (n = 2), and other clinical diagnostic criteria (n = 10). No patient in either arm received therapeutic defibrotide for VOD/SOS.

In a multivariate analysis, GO exposure was not associated with an increased risk of VOD/SOS (odds ratio [OR] 1.10, 95% CI: 0.43–2.81; $P = .85$), nor were any of the other factors considered in the analysis (Table 4 and Supplementary Table S2).

Secondary Outcomes

With a median ~8-year follow-up of survivors, 5-year survival probability (95% CI) was 38% (30–46%) in patients with GO exposure and 38% (34–42%) in controls (Table 3). For the corresponding groups of patients who developed VOD/SOS, 1-year survival probability (95% CI) was 33% (5–72%) and 27% (11–47%) from the onset of VOD/SOS (Supplementary Table S4). Three (3%) deaths in the GO group and 3 (<1%) deaths in the control group were attributed to VOD/SOS (Table 5). Five-year (95% CI) rates of DFS were 31% (24–39%) and 34% (30–38%) in GO-exposed patients and controls, respectively; corresponding 5-year relapse (95% CI) rates were 48% (39–56%) and 40% (36–44%) and 5-year NRM (95% CI) rates were 21% (15–29%) and 26% (22–30%) (Table 3).

In multivariate analyses, GO exposure was associated with an increased rate of relapse (HR 1.46, 95% CI: 1.11–1.93; $P = .007$) but was not significantly associated with OS (HR 1.08, 95% CI: 0.86–1.37; $P = .57$), DFS (HR 1.23, 95% CI: 0.98–1.53; $P = .07$), or NRM (HR 0.91, 95% CI: 0.64–1.29; $P = .58$; Table 4). Other factors associated with increased relapse were HCT-CI ≥3, poor cytogenetics, and a disease status of relapse or primary induction failure. Factors associated with decreased OS and DFS were age ≥50 years, HCT-CI ≥3, poor cytogenetics, a disease status of relapse or primary induction failure at the time of alloHCT, and a cord blood donor. Factors associated with increased NRM were age ≥50 years and a cord blood or other donor type (Table 4).

In an additional multivariate analysis, GO exposure was associated with an increased rate of grade 2–4 acute GVHD (HR 1.58, 95% CI 1.17–2.12; $P = .003$) but not chronic GVHD (HR 1.25, 95% CI: 0.96–1.63; $P = .09$).

Among patients with a total GO dose <10 mg versus ≥10 mg, respectively, who had available dosing data, 5-year survival probability (95% CI) was 25% (11–42%) and 39% (22–58%); 5-year (95% CI) rate of DFS was 19% (7–35%) versus 36% (19–54%), relapse 53% (36–71%) versus 50% (32–68%), and NRM 28% (13–46%) versus 14% (4–29%) (Supplementary Table S5). Formal statistical analyses to compare outcomes between dosing groups were not performed due to the sample size.

DISCUSSION

Hepatic VOD/SOS is a serious complication that occurs primarily following myeloablative alloHCT but has also been associated with the use of certain chemotherapies, including GO [3,7–9]. Results of this retrospective study showed the rate of VOD/SOS among adult patients who underwent myeloablative alloHCT for AML between 2008 and 2011, as reported to the CIBMTR, was similar in those with versus without prior GO exposure. Furthermore, after controlling for prognostic variables such as age, sex, disease status, cytogenetics, and conditioning regimen, GO exposure, at least in this cohort, did not

significantly increase the risk of developing VOD/SOS or death among patients who received myeloablative alloHCT.

In this study, the incidence of VOD/SOS among adult patients with GO exposure prior to alloHCT was 4%; 4 (3%) cases were classified as severe and 3 of 88 (3%) deaths were due to VOD/SOS. This rate is in accordance with another recent retrospective study, which also found a low incidence of post-transplant VOD/SOS (8%) in adult patients previously treated with GO, although the study included patients receiving either myeloablative or reduced-intensity conditioning [17]. Historically, the reported incidence of VOD/SOS in GO-exposed patients has been much higher; pooled data from 9 clinical trials published in 2006 or earlier revealed a rate of 37% after alloHCT in this population [8].

The low incidence of VOD/SOS observed here and in other recent reports may reflect a number of factors. Improvements in identifying and managing patient- and treatment-related VOD/SOS risk factors and advances in preventative therapeutic strategies over the past 2 decades have contributed to a general decline in the occurrence of VOD/SOS following alloHCT [4]. In addition, a shift away from the use of conditioning regimens containing dual alkylating agents or high doses of total body irradiation and toward the use of so-called “reduced toxicity myeloablative” busulfan/fludarabine-containing regimens has also contributed to this decreasing trend [4,6,18,19]. Specific to the cohort in our study, all patients received first alloHCT, which carries a lower risk of VOD/SOS compared with second or greater alloHCT [20]. Extending the interval between GO administration and alloHCT may also reduce risk [11]. In this study, the median time to alloHCT following GO was 4 months in patients in CR1, 7 months in patients in CR≥2, and 3 months in patients in relapse or with primary induction failure. Relatively long intervals between transplant and GO may have benefited these patients, particularly those in CR1 and CR≥2. Among the 6 patients in the GO arm who developed VOD/SOS, the median time from last GO dose to alloHCT was 3 months. Due to the relatively low rates of VOD/SOS, we were not able to demonstrate a relationship between time from last GO exposure to transplant and occurrence of VOD/SOS.

After controlling for a number of prognostic factors, GO exposure was not found to be a significant risk factor for the development of VOD/SOS or death in adult patients but was associated with an increased risk of relapse following alloHCT. An explanation for this latter finding is not immediately apparent. The risk of relapse depends on several factors, such as age, disease status prior to alloHCT, conditioning regimen, donor type, and cytogenetic and molecular markers [21–23]. In this study, these characteristics were generally well-balanced between treatment arms, although a slightly higher percentage of patients had poor cytogenetics in the GO (35%) versus control (27%) arm. Post-transplant outcomes in patients receiving GO prior to HCT have also been examined in the ALFA-0701 trial wherein no difference in relapse or NRM was observed between those who received GO prior to HCT versus those treated with standard chemotherapy alone [24]. However, patients in ALFA-0701 received fractionated-dose GO in combination with standard chemotherapy, whereas the patients in the current study were treated with GO using various dosages and administration schedules, thereby making a direct comparison difficult. It is worth noting that in the current analysis, GO exposure was associated with an increased risk of acute

GVHD. Earlier studies have shown reduced risk of relapse in patients developing GVHD, as GVHD develops via the same mechanism as the beneficial elimination of residual malignant cells known as the graft-versus-leukemia effect [25–27]. Therefore, our results suggest increased relapse in GO-exposed patients in this cohort is not the result of the blunting of the graft-versus-leukemia effect with GO treatment.

Consistent with prior reports [28–32], older age, HCT-CI ≥3, poor cytogenetics, disease status of relapse or primary induction failure at transplant, and cord blood transplants were significant predictors of poorer outcomes following alloHCT. However, no factors were found to be associated with increased VOD/SOS risk. In contrast, the CIBMTR recently published a systematic evaluation of VOD/SOS risk factors in which a number of prognostic factors were identified, including, but not limited to, young age, Karnofsky score, disease status, and conditioning regimen [33]. The lack of findings in the current analysis may be attributable to insufficient power, given the smaller sample size and low event rate. Among GO-exposed patients, those who received <10 mg versus ≥10 mg total GO dose had slightly lower rates of OS and DFS at 5 years and a slightly higher rate of NRM, which could be due, at least in part, to between-group differences in disease status and/or cytogenetics. Due to the sample size, formal statistical comparisons were not performed by dose.

The findings of this study are in contrast to a similar analysis recently reported in a pediatric population, which found GO to be a significant risk factor for the development of VOD/SOS and a higher incidence of VOD/SOS (16%) in GO-exposed pediatric patients compared with that observed here [34]. In a recent CIBMTR analysis, younger age was identified and then subsequently validated as being a strong adverse risk factor for the development of VOD/SOS [33]. The results of these two studies suggest that in the context of young children, who are at higher risk of VOD/SOS at baseline, the use of GO pre-HCT may be associated with an increased risk of VOD/SOS, whereas in adult patients without other risk factors for VOD/SOS, the incremental risk of VOD/SOS after the modern day myeloablative conditioning transplant may not be evident without studying a very large cohort.

A few limitations of this analysis should be noted. First, VOD/SOS, especially milder cases, may have been under-reported due to the retrospective nature of the study. However, VOD/SOS is a serious illness that is usually recorded in medical records and likely would have been systematically reported to the CIBMTR. Variability in methods for ascertaining VOD/SOS could also have contributed to under-reporting of VOD/SOS in this population [4]. Lastly, it is possible that patients who received a lower GO dose or had more remote exposure (i.e., a longer interval between last GO dose and alloHCT) were more likely to be offered myeloablative alloHCT, thereby introducing an element of selection bias to this analysis.

In conclusion, we found that adult patients with AML who received GO prior to myeloablative alloHCT in recent years had a low incidence of post-transplant VOD/SOS, and exposure to GO was not associated with an increased risk of VOD/SOS or death. Our results suggest that prior use of GO should not, in itself, preclude adult patients without other obvious VOD/SOS risk factors from receiving myeloablative alloHCT in the current era. Nonetheless, physicians should continue to be vigilant in their monitoring of VOD/SOS

in patients who undergo alloHCT, especially in those who have received prior GO therapy. Prospective studies are planned to evaluate the relationship of GO with VOD/SOS in patients receiving alloHCT in the era of fractionated GO dosing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- VOD/SOS incidence at 100 days post HCT was 4% vs 3% in GO-exposed adults vs controls.
- Five-year overall survival probability was 38% in both groups.
- GO exposure before HCT was not associated with an increased risk of VOD/SOS or death.

Table 1.

Patient-, disease-, and transplant-related characteristics

n (%)*	GO n =137	Control n = 548	*P* Value
Patient-related			
Age at transplant, median (range), years	42 (18–73)	38 (18–74)	.26
Male	62 (45)	291 (53)	.10
Karnofsky performance score			.06
90–100	79 (58)	346 (63)	
<90	52 (38)	194 (35)	
Not reported	6 (4)	8 (1)	
HCT-CI			.97
0	54 (39)	224 (41)	
1–2	(25)	137 (25)	
≥3	46 (34)	175 (32)	
Not reported	3 (2)	12 (2)	
Hepatitis B and C serostatus pre-HCT			.66
B and C positive	4 (3)	20 (4)	
B positive	1 (<1)	6 (1)	
B and C negative	129 (94)	501 (91)	
Not tested/inconclusive	3 (2)	21 (4)	
Disease-related			
Cytogenetics†			.03
Favorable	9 (7)	65 (12)	
Intermediate	80 (58)	322 (59)	
Poor	48 (35)	149 (27)	
Not reported	0	12 (2)	
Disease status			.99
First complete remission	45 (33)	180 (33)	
Second or greater complete remission	41 (30)	164 (30)	
Relapse/primary induction failure	51 (37)	204 (37)	
Transplant-related			
Conditioning regimen			.64
Myeloablative-total body irradiation	56 (41)	236 (43)	
Myeloablative-chemotherapy	81 (59)	312 (57)	
Pharmacokinetics for busulfan‡	40 (52)	143 (45)	
Time from receiving GO to transplant, median (range), mo			–
First complete remission	4(2–10)	–	
Second or greater complete remission	7 (1–52)	–	
Relapse/primary induction failure	3 (<1–76)	–	
Type of donor.			.74
Related	37 (27)	170 (31)	

n (%)*	GO n =137	Control n = 548	*P* Value
Unrelated	73 (53)	275 (50)	
Single cord blood	7 (5)	27 (5)	
Double cord blood	20 (15)	79 (14)	
Donor-recipient CMV match			.55
Negative, negative	31 (23)	116 (21)	
Positive, negative	15 (11)	56 (10)	
Negative, positive	49 (36)	169 (31)	
Positive, positive	38 (28)	181 (33)	
Not reported	4 (3)	26 (5)	
Donor age, median (range), years§	32 (19–57)	31 (19–60)	.40
Graft type			.58
Bone marrow	21 (15)	68 (12)	
Peripheral blood	89 (65)	374 (68)	
Umbilical cord blood	27 (20)	106 (19)	
GVHD prophylaxis			.43
Tacrolimus-based	104 (76)	406 (74)	
Cyclosporine-based	32 (23)	123 (22)	
Other	1 (<1)	19 (3)	
Sirolimus usage	4 (3)	45 (8)	.03
ATG/alemtuzumab			.67
ATG alone	35 (26)	142 (26)	
Alemtuzumab alone	2 (1)	3 (<1)	
No ATG OI alemtuzumab	100 (73)	402 (73)	
Not reported	0	1 (<1)	
Year of transplant			<.001
2008	64 (47)	174 (32)	
2009	47 (34)	169 (31)	
2010	23 (17)	138 (25)	
2011	3 (2)	67 (12)	
Follow-up of survivors, median (range), months	96 (11–123)	92 (3–124)	

*Unless otherwise noted.

†Cytogenetic classification was defined as follows:
Favorable: inv(16), t(16;16), del(16q), t(15;17), [t(8;21) without del(9q) or complex].
Intermediate: normal karyotype, +8, +6, -y, del(12p), t(9;11), 11q23, MLL rearranged, and any other abnormalities not belonging to favorable or poor.
Poor: complex (≥3 abnormalities), −5/5q, −7/7q, abn 3q 9q 11q 21q 17p, t(6;9), t(9;22).

‡For busulfan-containing regimens only.

§For unrelated donors only.

ATG indicates antithymocyte globulin; CMV, cytomegalovirus; GO, gemtuzumab ozogamicin; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation-comorbidity index; MLL, mixed lineage leukemia

Table 2.

Patient-, disease-, and transplant-related characteristics by GO total dose

n (%)*	GO <10 mg Total Dose n = 30	GO ≥10 mg Total Dose n = 28
Patient-related		
Age at transplant, median (range), years	41 (19–63)	47 (21–70)
Males	15 (50)	13 (46)
Karnofsky performance score		
90–100	16 (53)	15 (54)
<90	13 (43)	13 (46)
Not reported	1 (3)	0
HCT-CI		
0	13 (43)	9 (32)
1–2	9 (30)	9 (32)
≥3	8 (27)	10 (36)
Hepatitis B and C serostatus pre-HCT		
B and C positive	0	1 (4)
B positive	1 (3)	0
B and C negative	28 (93)	26 (93)
Not tested/inconclusive	1 (3)	1 (4)
Disease-related		
Cytogenetics†		
Favorable	1 (3)	2 (7)
Intermediate	16 (53)	20 (71)
Poor	13 (43)	6 (21)
Disease status		
First complete remission	12 (40)	8 (29)
Second or greater complete remission	8 (27)	9 (32)
Relapse/primary induction failure	10 (33)	11 (39)
Transplant-related		
GO administration		
Single-agent GO	0	0
GO plus chemotherapy	30 (100)	28 (100)
Fractionated dosing	8 (27)	11 (39)
Cycles of GO before HCT, median (range)	1 (1–3)	1 (1–3)
Time from receiving GO transplant, median (range), months	4 (1–12)	3 (1–15)
Conditioning regimen		
Myeloablative–total body irradiation	9 (30)	9 (32)
Myeloablative–chemotherapy	21 (70)	19 (68)
Pharmacokinetics for busulfan‡	7 (41)	10 (53)
Time from receiving GO to transplant, median (range), months		

n (%)*	GO <10 mg Total Dose n = 30	GO ≥10 mg Total Dose n = 28
First complete remission	4 (2–7)	3 (3–7)
Second or greater complete remission	4 (2–9)	6 (2–15)
Relapse/primary induction failure	4 (1–12)	2 (1–51)
Type of donor		
Related	11 (37)	12 (43)
Unrelated	11 (37)	15 (54)
Single cord blood	2 (7)	1 (4)
Double cord blood	6 (20)	0
Donor-recipient CMV match		
Negative, negative	4 (13)	10 (36)
Positive, negative	5 (17)	2 (7)
Negative, positive	12 (40)	6 (21)
Positive, positive	9 (30)	8 (29)
Not reported	0	2 (7)
Donor age, median (range), years§	33 (25–45)	28 (19–44)
Graft type		
Bone marrow	4 (13)	7 (25)
Peripheral blood	18 (60)	20 (71)
Umbilical cord blood	8 (27)	1 (4)
GVHD prophylaxis		
Tacrolimus-based	21 (70)	27 (96)
Cyclosporine-based	8 (27)	1 (4)
Other	1 (3)	0
Sirolimus usage	1 (3)	0
ATG/alemtuzumab		
ATG alone	7 (23)	5 (18)
Alemtuzumab alone	1 (3)	0
No ATG or alemtuzumab	22 (73)	23 (82)
Year of transplant		
2008	12 (40)	.4 (50)
2009	13 (43)	9 (32)
2010	5 (17)	4 (14)
2011	0	1 (4)
Follow-up of survivors, median (range), months	93 (49–98)	96 (56–121)

*Unless otherwise noted.

†Cytogenetic classification was defined as follows:
Favorable: inv(16), t(16;16), del(16q), t(15;17), [t(8;21) without del(9q) or complex].
Intermediate: normal karyotype, +8, +6, –y, del(12p), t(9;11), 11q23, MLL rearranged, and any other abnormalities not belonging to favorable or poor.
Poor: complex (≥3 abnormalities), –5/5q, –7/7q, abn 3q 9q 11q 21q 17p, t(6;9), t(9;22).

‡For busulfan-containing regimens only.

[§] For unrelated donors only.

ATG indicates antithymocyte globulin; CMV, cytomegalovirus; GO, gemtuzumab ozogamicin; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation-comorbidity index; MLL, mixed lineage leukemia

Table 3.

Outcomes in all patients

Outcomes, % (95% CI)*	GO n = 137	Controls n = 548	*P* Value
VOD/SOS			
Patients who developed VOD/SOS, n	6	22	-
VOD/SOS at 100 days	4 (1–7)	3 (2–5)	.76
Severe VOD/SOS at 100 days	3 (1–6)	1 (0–2)	.18
Overall survival			
100 days	80 (73–86)	81 (78–84)	.81
6 months	66 (58–74)	69 (65–73)	.52
1 year	53 (44–61)	57 (53–61)	.33
3 years	41 (33–49)	42 (38–46)	.83
5 years	38 (30–46)	38 (34–42)	.97
Disease-free survival			
1 year	45 (36–53)	49 (45–54)	.31
3 years	34 (26–42)	38 (34–42)	.45
5 years	31 (24–39)	34 (30–38)	.46
Relapse			
1 year	40 (32–48)	32 (28–36)	.09
3 years	45 (37–54)	38 (34–42)	.13
5 years	48 (39–56)	40 (36–44)	.10
Nonrelapse mortality			
1 year	15 (10–22)	18 (15–22)	.37
3 years	21 (14–28)	24 (21–28)	.34
5 years	21 (15–29)	26 (22–30)	.26

*From date of transplant.

CI indicates confidence interval; GO, gemtuzumab ozogamicin; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome

Table 4.

Multivariate analysis of outcomes

	VOD/SOS at 100 Days		OS		DFS		Relapse		NRM	
	OR		HR		HR		HR		HR	
Covariates*	**(95% CI)**	***P***	**(95% CI)**	***P***	**(95% CI)**	***P***	**(95% CI)**	***P***	**(95% CI)**	***P***
GO exposure										
GO vs. no GO	1.10 (0.43–2.81)	.85	1.08 (0.86–1.37)	.57	1.23 (0.98–1.53)	.07	1.46 (1.11–1.93)	.007	0.91 (0.64–1.29)	.58
Age, years										
≥50 vs. <50	–	–	1.39 (1.14–1.69)	.001	1.33 (1.10–1.61)	.003	–	–	1.88 (1.35–2.62)	<.001
HCT-CI										
≥3 vs. 0–2	–	–	1.43 (1.20–1.72)	<.001	1.41 (1.18–1.70)	<.001	1.43 (1.12–1.83)	.004	–	–
Cytogenetics										
Poor vs. favorable/intermediate	–	–	1.27 (1.04–1.54)	.021	1.33 (1.10–1.62)	.004	1.51 (1.18–1.92)	.004	–	–
Disease status										
Relapse/PIF vs. CR1	–	–	2.30 (1.82–2.92)	<.001	2.51 (1.99–3..8)	<.001	3.56 (2.64–4.79)	<.001	–	–
Type of donor										
Cord blood vs. HLA-identical sibling	–	–	1.63 (1.22–2.17)	.001	1.51 (1.16–1.96)	.002	–	–	3.22 (2.02–5.13)	<.001
Other vs. HLA-identical sibling	–	–	–	–	–	–	–	–	2.36 (1.46–3.79)	<.001

OR/HR >1 indicates a worse outcome for the comparison (first) group.

*Significant covariates ($P < .05$) reported with the exception of GO exposure, which is reported for all outcomes regardless of significance.

CI indicates confidence interval; CR, complete remission; GO, gemtuzumab ozogamicin; HCT-CI, hematopoietic cell transplantation-comorbidity index; HLA, human leukocyte antigen; HR, hazard ratio; NRM, nonrelapse mortality; OR, odds ratio; PIF, primary induction failure; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome

Table 5.

Death summary

Cause, n (%)	GO n = 137	Controls n = 548
Total deaths	88	355
Primary disease	48 (55)	185 (52)
Graft failure	0	6 (2)
GVHD	10 (11)	29 (8)
Infection	9 (10)	46 (13)
Interstitial pneumonia/ARDS	1 (1)	16 (5)
Organ failure		
VOD/SOS	3 (3)	3 (<1)
Liver failure	1 (1)	3 (<1)
Cardiac failure	2 (2)	9 (2)
Pulmonary failure	3 (3)	13 (4)
CNS failure	0	1 (<1)
Renal failure	0	1 (<1)
Multiple organ failure	2 (2)	8 (2)
Organ failure, not specified	1 (1)	4 (1)
Secondary malignancy	0	6 (2)
Hemorrhage	2 (2)	7 (2)
Other	1 (1)	8 (2)
Not reported	5 (6)	10 (3)

ARDS indicates acute respiratory distress syndrome; CNS, central nervous system; GO, gemtuzumab ozogamicin; GVHD, graft-versus-host disease; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome