HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

Pediatr Blood Cancer. 2021 August ; 68(8): e29067. doi:10.1002/pbc.29067.

Veno-occlusive disease risk in pediatric patients with acute myeloid leukemia treated with gemtuzumab ozogamicin before allogeneic hematopoietic cell transplantation

Christine Duncan[1], **Andrew St. Martin**[2], **Waleska S. Pérez**[2], **Patricia Steinert**[2], **Mei-Jie Zhang**[2,3], **Deborah Chirnomas**[4], **Caroline J. Hoang**[4], **Fausto R. Loberiza Jr**[4], **Wael Saber**[2]

[1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA

[2]CIBMTR® (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

[3]Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI, USA

[4]Pfizer Inc, New York, NY, USA

Abstract

Background: Gemtuzumab ozogamicin (GO) administered before allogeneic hematopoietic cell transplantation (alloHCT) has been linked to an increased risk of hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS).

Procedure: This retrospective analysis examined VOD/SOS risk and clinical outcomes in pediatric patients with acute myeloid leukemia who received myeloablative alloHCT in 2008–2011 with (n = 148) and without (n = 348; controls) prior GO exposure and were reported to the Center for International Blood and Marrow Transplant Research.

Results: Cumulative incidences (95% confidence interval) of VOD/SOS and severe VOD/SOS, respectively, at 100 days were 16% (11–23) and 8% (4–13) for GO-exposed patients and 10% (7–13) and 3% (2–5) for controls. With a median follow-up of approximately 7 years, the 5-year

Corresponding author: Wael Saber, MD, MS, CIBMTR, Froedtert and the Medical College of Wisconsin Clinical Cancer Center, 9200 W. Wisconsin Avenue, Suite C5500, Milwaukee, WI 53226, USA. Tel: +1 414 805 0700; Fax: +1 414 805 0714, wsaber@mcw.edu.

Conflict of interest

DC was an employee of Pfizer at the time of manuscript development. CJH and FRL are employees of and have equity ownership in Pfizer. CD, ASM, WSP, PS, M-JZ, and WS declare no competing interests.

These data were published in part in meeting abstracts:

1. Duncan C, St. Martin A, Perez W, Steinert P, Zhang M-J, Chirnomas SD, Hoang CJ, Loberiza F, Saber W. Veno-Occlusive Disease (VOD) Characteristics in Pediatric Patients (Pts) With Acute Myeloid Leukemia (AML) Receiving Gemtuzumab Ozogamicin (GO) Before Allogeneic Stem Cell Transplant (SCT). *Biology of Blood and Marrow Transplantation*. 2018;24(3, supplement):S302. Presented at the 2018 Blood and Marrow Transplantation (BMT) Tandem Meetings, February 21–25, 2018

2. Duncan C, St. Martin A, Perez W, Steinert P, Zhang M-J, Chirnomas SD, Hoang CJ, Loberiza F, Saber W. Veno-Occlusive Disease (VOD) Characteristics in Pediatric Patients With Acute Myeloid Leukemia (AML) Receiving Gemtuzumab Ozogamicin (GO) Before Allogeneic Stem Cell Transplant (SCT). *Bone Marrow Transplantation*. 2019;53:145–805:P063. Presented at the 44th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT), March 18–21, 2018.

adjusted overall survival probability (95% confidence interval) after alloHCT was 51% (43–58) and 55% (50–60) for GO-exposed patients and controls, respectively; three (4%) and one (<1%) deaths were attributed to VOD/SOS. In multivariate analyses, GO exposure was observed to be associated with an increased risk of VOD/SOS at 100 days but was not associated with overall survival, disease-free survival, relapse, or nonrelapse mortality.

Conclusions: Results suggest that GO treatment prior to alloHCT in pediatric patients may increase the risk of VOD/SOS but not death.

Keywords

gemtuzumab ozogamicin; veno-occlusive disease; sinusoidal obstruction syndrome; pediatric; hematopoietic cell transplantation; acute myeloid leukemia

INTRODUCTION

Acute myeloid leukemia (AML) is the second-most common childhood leukemia, with an estimated 5-year survival rate of 64% among children aged 0–19 years.[1] A promising approach to the treatment of pediatric AML is targeted therapy such as gemtuzumab ozogamicin (GO). GO is an antibody drug conjugate consisting of a potent humanized monoclonal antibody against the CD33 antigen, which is expressed by leukemic blasts in most patients with AML,[2] covalently linked to the cytotoxic antitumor antibiotic N-acetyl-γ-calicheamicin. However, there are concerns over the risk of hepatotoxicity, particularly hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), with GO therapy.[3]

VOD/SOS is a potentially life-threatening complication primarily observed following hematopoietic cell transplantation (HCT), and is more common after myeloablative allogeneic HCT (alloHCT) than reduced-intensity alloHCT or autologous HCT.[4–6] Compared with adults, pediatric patients have a higher risk of developing VOD/SOS,[7] which may be attributable to a number of factors such as immaturity of the liver and differences in the underlying diseases being treated.[8] VOD/SOS may have a different clinical presentation in pediatric patients; for example, late-onset and anicteric VOD/SOS are observed more frequently.[8] The average incidence of post-transplant VOD/SOS is reported to be 20% in children.[8] However, the incidence of VOD/SOS after alloHCT has been decreasing in recent years due to advances in transplantation techniques, improved patient selection, and increased use of reduced-intensity and less-toxic conditioning regimens.[4,9]

GO treatment before alloHCT may increase VOD/SOS risk.[10] The rate of VOD/SOS in pediatric patients who received GO and subsequent HCT has been reported to be as high as 40%.[11] GO was first approved in the United States in 2000 for older adults with AML in first relapse at a dose of 9 mg/m^2. It was voluntarily withdrawn from the US market in 2010 after a confirmatory phase 3 study failed to demonstrate the clinical benefit of GO in combination with chemotherapy versus chemotherapy alone in the front-line setting and reported a higher rate of early deaths in the GO arm.[12,13] Lower, fractionated dosing strategies have been examined as a way to mitigate the risk of toxicity while maintaining efficacy of GO. The phase 3 ALFA-0701 trial demonstrated improved outcomes in adults

with de novo AML administered fractionated-dose GO (3 mg/m^2 on Days 1, 4, and 7 of induction and Day 1 of each of two courses of consolidation) in combination with standard chemotherapy versus standard chemotherapy alone.[14] The incidence of VOD/SOS in patients receiving GO was low overall[14] and in the subset of patients who received alloHCT.[15] Another phase 3 trial reported the addition of GO (3 mg/m^2 on Day 6 of induction course 1 and Day 7 of intensification course 2) to chemotherapy versus chemotherapy alone in patients aged 0–29 years significantly improved event-free survival through a reduction in relapse, with no significant differences in VOD/SOS incidence between arms.[16] In 2017, GO was approved by the US Food and Drug Administration (FDA) for the treatment of newly diagnosed CD33+ AML in adults and relapsed/refractory CD33+ AML in adult and pediatric (aged ≥2 years) patients. The approval included a different patient population and a lower recommended dose and revised schedule compared with the 2000 approval.[17]

A prior analysis of data from the Center for International Blood and Marrow Transplantation Research (CIBMTR) indicated GO exposure before myeloablative alloHCT did not increase VOD/SOS risk in adults who received alloHCT in 2008–2011.[18]

Herein, we utilized the CIBMTR database for the same time period to examine VOD/SOS incidence and post-transplant outcomes in pediatric patients who received myeloablative alloHCT with and without prior GO exposure. At the time, GO treatment in pediatric patients was off-label but consistent with the original approved dosing regimen of 9 mg/m^2 in older adults. Our objective was to report the real-world experience of post-transplant outcomes in pediatric patients treated with GO prior to the new 2017 dosing regimen.

METHODS

Data source

The CIBMTR (www.CIBMTR.org) is a research collaboration between the Medical College of Wisconsin (Milwaukee, WI) and the National Marrow Donor Program® / Be The Match® (Minneapolis, MN) and 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 and has data for more than 495 000 transplant recipients and receives data for more than 24 000 new transplants each year.

Study design

This retrospective analysis included pediatric patients (aged ≤18 years) with AML who underwent first myeloablative alloHCT between 2008 and 2011 (prior to the 2017 FDA approval of GO) with or without prior GO exposure and were reported to the CIBMTR at the Comprehensive Report Form level. Patient records selected with a weighted randomization scheme to report at the Comprehensive Report Form level of data collection capture detailed patient-, disease-, and treatment-related data in addition to the standard data collection. All data were collected pretransplant, 100 days, and 6 months after transplant; annually until 6 years after transplant; then biannually until death. The classification of

conditioning intensity was based on Bacigalupo[19] and is summarized in Supplemental Table S1.

This analysis was limited to patients who received myeloablative conditioning intensity based on the low incidence of VOD/SOS events in the reduced-intensity cohort. The cutoff year of 2011 was chosen due to the small sample size of patients who received alloHCT with prior GO exposure 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 excluded from the analysis. Patients were not matched between arms because there were not enough controls for every GO-exposed pediatric patient to have at least three matches. All patient records that fulfilled the eligibility criteria were included in the analysis. No patient in this study received prophylactic defibrotide.

Outcomes

The primary outcome was the incidence of VOD/SOS at 100 days following alloHCT. VOD/SOS diagnosis was reported by individual centers and was based on the modified Seattle criteria,[20] the Baltimore criteria,[21] autopsy, biopsy, or a combination of the following criteria: ascites, serum bilirubin >2.0 mg, elevated liver enzymes, abnormal ultrasonography, and weight gain. Severe VOD/SOS was defined as VOD/SOS associated with renal impairment requiring dialysis and/or any noninfectious pulmonary abnormality.

Secondary outcomes were these time-to-event endpoints: (1) overall survival (OS) – time from transplant to death due to any cause; patients were censored at time of last contact; (2) relapse – time from transplant to morphologic, cytogenetic, or molecular recurrence of disease; patients alive without disease recurrence were censored at last contact; (3) disease-free survival (DFS) – time from transplant to death or relapse; patients alive and in remission were censored at last contact; and (4) nonrelapse mortality (NRM) – time from transplant to death occurring in continuous complete remission (CR); patients alive and in remission were censored at last contact. Probability of OS is reported at 100 days, 6 months, and 1, 3, and 5 years; probabilities of DFS, relapse, and NRM are reported at 1, 3, and 5 years.

Statistical methods

The cumulative incidences of VOD/SOS and severe VOD/SOS at 100 days were estimated using the cumulative incidence estimator, adjusted for the competing risk of death without VOD/SOS. 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. Death in remission was treated as the competing risk for relapse, whereas relapse was treated as the competing risk for NRM. Multivariate analyses were performed for VOD/SOS at 100 days, OS, DFS, relapse, and NRM. A logistic regression model was used to compare the incidence of VOD/SOS at Day 100 between GO-exposed patients and controls. 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 age at transplant, sex, Karnofsky performance score, HCT-specific comorbidity index, hepatitis B and C serostatus prior to transplant, cytogenetics, disease status prior to transplant, conditioning intensity, conditioning regimen, pharmacokinetics (PK) of busulfan, donor

type, donor-recipient cytomegalovirus status, donor age (for unrelated adult donors only), graft type, graft-versus-host disease prophylaxis, sirolimus usage, antithymocyte globulin/alemtuzumab usage, and year of transplant. A stepwise model building approach was used. All factors with $P < 0.05$ were retained in the final models, with the exception of GO exposure, which was retained in all steps of the model building regardless of significance level. Adjusted survival probability and adjusted cumulative incidence estimates were generated from the final regression models stratified on treatment and weighted averages of covariate values using the pooled sample proportion as the weight function. These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors.[22,23]

RESULTS

Patients and treatment

A total of 148 pediatric patients with GO exposure and 348 without GO exposure (controls) before myeloablative alloHCT were included in the analysis; 85% of patients received alloHCT in the United States. Median (range) age at transplant was 9 (<1–18) years in the GO-exposed group and 8 (<1–18) years in the control group (Supplemental Table S2). Patient- and disease-related characteristics were generally balanced between groups, but a higher proportion of controls (57%) versus GO-exposed patients (42%) were in first CR (CR1) prior to transplant.

GO dosing data were available for 74 (50%) GO-exposed patients. Characteristics were generally balanced between patients with and without available dosing data, although patients with dosing data were less likely to have received antithymocyte globulin (Supplemental Table S3). Median (range) total GO dose was 3.0 (1.4–12) mg/m^2, and all patients received GO in combination with chemotherapy.

Incidence of VOD/SOS

The cumulative incidences (95% confidence interval [CI]) of VOD/SOS and severe VOD/SOS, respectively, at 100 days were 16% (11–23) and 8% (4–13) for GO-exposed patients, and 10% (7–13) and 3% (2–5) for controls (Table 1). In all, 28 patients in the GO-exposed group and 37 patients in the control group developed VOD/SOS after alloHCT; of these, 8 (29%) and 11 (30%) received therapeutic defibrotide. Diagnosis of VOD/SOS was confirmed using autopsy/biopsy (GO: $n = 3$; control: $n = 4$), the Baltimore criteria (GO: $n = 16$; control: $n = 16$), the modified Seattle criteria (GO: $n = 3$; control: $n = 3$), and other clinical diagnostic criteria (GO: $n = 6$; control: $n = 14$).

In the multivariate analysis, GO exposure versus no GO exposure and chemotherapy-based conditioning with PK monitoring of busulfan versus total body irradiation (TBI)-based conditioning were observed to be associated with increased risk of VOD/SOS at 100 days (Table 2). We observed that a shorter interval between GO and HCT was not associated with increased rates of VOD/SOS at 100 days (Supplemental Table S4).

Post-transplant secondary outcomes

With a median follow-up of approximately 7 years, the 5-year adjusted OS probability (95% CI) after alloHCT was 51% (43–58) and 55% (50–60) for GO-exposed patients and controls, respectively (Table 1). In patients who developed VOS/SOS, 1-year OS probability (95% CI) after VOD/SOS onset was 39% (22–58) for GO-exposed patients and 54% (38–70) for controls (Supplemental Table S5). Three (4%) deaths in the GO-exposed group and one (<1%) death in the control group were due to VOD/SOS (Table 3). Five-year adjusted probability (95% CI) of NRM was 18% (12–24) and 15% (12–20), relapse 37% (30–44) and 37% (32–41), and DFS 42% (35–50) and 48% (43–53) for GO-exposed patients and controls, respectively (Table 1).

Factors observed to be predictive of worse OS ($P < 0.05$) were HCT-specific comorbidity index ≥3 versus 0–2, intermediate/poor versus favorable cytogenetics, and disease status of relapse/primary induction failure versus CR1 prior to transplant. Disease status of relapse/primary induction failure versus CR1 was observed to be predictive of decreased DFS, and chemotherapy-based conditioning with PK monitoring of busulfan versus TBI-based conditioning predictive of increased NRM. Factors observed to be predictive of increased relapse were a bone marrow or peripheral blood versus umbilical cord blood graft and disease status of relapse/primary induction failure versus CR1 prior to alloHCT. GO exposure was not observed to be significantly associated with any secondary outcomes (Table 2).

DISCUSSION

In this retrospective analysis of outcomes in pediatric patients with AML receiving myeloablative alloHCT, prior treatment with GO was observed to be associated with an increased risk of developing VOD/SOS, but post-transplant OS, DFS, relapse, and NRM did not differ between those with and without prior GO treatment.

We observed cumulative incidences of VOD/SOS and severe VOD/SOS at 100 days of 16% and 8%, respectively, in pediatric patients with GO exposure before alloHCT compared with 10% and 3% in the control group. A greater proportion of controls versus GO-exposed patients were in CR1 before transplant, yet GO exposure was observed to be associated with increased VOD/SOS risk even after controlling for disease status and other relevant factors. Although the GO-exposed group had a higher incidence of VOD/SOS, few cases ($n = 3$) were fatal.

Our findings are consistent with a prior report in which four of 28 patients (14%) aged <21 years received HCT after GO and developed VOD/SOS; two cases were considered severe, and all patients recovered.[24] Another study reported a VOD/SOS rate of 40% in pediatric patients aged 1–16 years who received single-agent GO (two doses of 6–9 mg/m^2) and underwent subsequent HCT.[11] However, the study population was limited to patients with multiple relapsed or primary refractory AML and most patients received HCT <3.5 months after last GO dose, a potential risk factor for VOD/SOS.[25] In our study, median time from last GO dose to transplant was 4 months for those in CR1 and 6 months for those in CR≥2 or

relapse/primary induction failure. However, we did not observe an association between the time interval between GO and HCT and VOD/SOS at 100 days in this cohort.

A separate analysis of CIBMTR data found a lower incidence of VOD/SOS (4%) in adults with AML who received alloHCT with prior GO exposure compared with that observed in the current report in children. Furthermore, GO exposure was not observed to be a significant risk factor for the development of VOD/SOS in the adult cohort.[18] Our findings are consistent with a general trend of higher VOD/SOS incidence in children compared with adults across disease areas and a prior CIBMTR analysis which identified and validated younger age as a strong adverse risk factor for the development of VOD/SOS.[7,8] Based on increasing evidence of differences in the incidence, genetic predisposition, clinical presentation, and outcomes of VOD/SOS in pediatric compared with adult patients, the European Society for Blood and Marrow Transplantation recently developed separate diagnostic and severity criteria for pediatric patients.[8] However, these criteria were not published until 2018 and therefore not utilized in this study.

The only other factor observed to be associated with increased VOD/SOS risk was chemotherapy-based conditioning with PK monitoring of busulfan versus TBI-based conditioning, which was also associated with increased NRM. Although PK monitoring is intended to reduce the toxicity of busulfan-containing regimens,[26] our results suggest that TBI-based conditioning still carries a lower risk of VOD/SOS in children. Variables associated with decreased OS included HCT-specific comorbidity index ≥3, intermediate and poor cytogenetics, and a disease status of relapse/primary induction failure at alloHCT, the latter of which was also associated with lower DFS and higher relapse. These results are consistent with previous findings of poorer outcomes in patients with these characteristics.[27,28] Notably, GO exposure was not observed to be associated with an increased risk of death despite carrying a higher risk for the development of VOD/SOS. The proportion of patients receiving therapeutic defibrotide was balanced between groups and therefore defibrotide use likely did not affect these results. Furthermore, GO exposure was not observed to be predictive of DFS, relapse, or NRM. Although we observed no differences in survival outcomes between patient groups, the AAML0531 trial demonstrated a benefit in DFS and OS in GO-treated versus non–GO-treated children and adolescents who received HCT for AML. However, AAML0531 was restricted to patients with intermediate-risk AML in first remission, and all patients in the GO arm received GO 3 mg/m^2 in combination with chemotherapy.[16] Therefore, a cross-study comparison is complicated by differences in dosing and disease characteristics.

Study limitations included the retrospective study design and variability in diagnostic methods, which could have contributed to underreporting or inconsistent reporting.[4] However, VOD/SOS is a serious illness that is usually recorded in medical records and likely would have been systematically reported to the CIBMTR. Additionally, many patient records were missing GO dosing information. The FDA-approved regimen at the time these patients were treated was 9 mg/m^2 for adults aged ≥60 years in first relapse, but we cannot be certain how many patients with missing data in this study received a higher or lower dose, especially given the off-label use in children.

GO is currently approved in the United States for the treatment of adults and pediatric patients (aged ≥1 month) with newly diagnosed CD33+ AML and adult and pediatric (aged ≥2 years) patients with relapsed/refractory CD33+ AML.[29] The current recommended dosing regimen for adults with newly diagnosed CD33+ AML is 3 mg/m^2 (up to one 4.5-mg vial) on Days 1, 4, and 7 of induction and Day 1 of each of two consolidation courses in combination with chemotherapy or 6 mg/m^2 on Day 1 and 3 mg/m^2 on Day 8 of induction and up to eight continuation courses of 2 mg/m^2 on Day 1 every 4 weeks as a single agent; for pediatric patients with newly diagnosed AML, the recommended dosing regimen is 3 mg/m^2 for patients with body surface area (BSA) ≥0.6 m^2 or 0.1 mg/kg for patients with BSA <0.6 mg/m^2. The recommended dosing regimen for CD33+ relapsed/refractory AML, adults and pediatric patients, is 3 mg/m^2 on Days 1, 4, and 7 as a single-agent. The original dose of 9 mg/m^2 is no longer approved for use in the United States due to the higher risk of toxicity. Although this cohort received GO based on the old dosing regimen, this analysis establishes a baseline of VOD/SOS risk with GO use in pediatric patients that may be used going forward to compare with the risk associated with the current recommended dosing regimen.

In conclusion, pediatric patients with AML who received GO before myeloablative alloHCT in 2008–2011 were observed to have an increased risk of VOD/SOS. Despite this, OS was similar between those with and without GO exposure, and few fatal cases of VOD/SOS were observed in the GO-exposed group. Nonetheless, these findings indicate that physicians should take caution when considering alloHCT for AML in pediatric patients with prior GO treatment. Further monitoring and reporting will clarify whether the new 2017 dosing regimen results in a reduced rate of VOD/SOS in pediatric patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was sponsored by Pfizer. Medical writing support was provided by Emily Balevich, PhD, of Engage Scientific Solutions and was funded by Pfizer. The CIBMTR is supported primarily by Public Health Service U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); HHSH250201700006C, and HHSH250201700007C from the Health Resources and Services Administration (HRSA); and N00014-20-1-2705 and N00014-20-1-2832 from the Office of Naval Research.

Data sharing statement

CIBMTR supports accessibility of research in accord with the National Institutes of Health Data Sharing Policy and theNational Cancer Institute 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 July 1, 2019, and in accordance with journal embargo policy, CIBMTR will make available on its public website de-identified analysis datasets and corresponding data dictionaries.

Abbreviation key

alloHCT	allogeneic hematopoietic cell transplantation

AML	Acute myeloid leukemia
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplantation Research
CR1	first complete remission
CR	Complete remission
DFS	Disease-free survival
FDA	US Food and Drug Administration
GO	gemtuzumab ozogamicin
HCT	hematopoietic cell transplantation
NRM	Nonrelapse mortality
OS	Overall survival
PK	pharmacokinetics
TBI	Total body irradiation
VOD/SOS	veno-occlusive disease/sinusoidal obstruction syndrome

REFERENCES

1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64:83–103. [PubMed: 24488779]
2. Ehninger A, Kramer M, Rollig C, et al. Distribution and levels of cell surface expression of CD33 and CD123 in acute myeloid leukemia. Blood Cancer J 2014;4:e218. [PubMed: 24927407]
3. Giles FJ, Kantarjian HM, Kornblau SM, et al. Mylotarg (gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. Cancer 2001;92:406–413. [PubMed: 11466696]
4. Carreras E, Diaz-Beya M, Rosinol L, et al. The incidence of veno-occlusive disease following allogeneic hematopoietic stem cell transplantation has diminished and the outcome improved over the last decade. Biol Blood Marrow Transplant 2011;17:1713–1720. [PubMed: 21708110]
5. Carreras E. How I manage sinusoidal obstruction syndrome after haematopoietic cell transplantation. Br J Haematol 2015;168:481–491. [PubMed: 25401997]
6. Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant 2010;16:157–168. [PubMed: 19766729]
7. Strouse C, Zhang Y, Zhang MJ, et al. Risk score for the development of veno-occlusive disease after allogeneic hematopoietic cell transplant. Biol Blood Marrow Transplant 2018;24:2072–2080. [PubMed: 29928989]
8. Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation. Bone Marrow Transplant 2018;53:138–145. [PubMed: 28759025]
9. Dalle JH, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. Biol Blood Marrow Transplant 2016;22:400–409. [PubMed: 26431626]

10. McKoy JM, Angelotta C, Bennett CL, et al. Gemtuzumab ozogamicin-associated sinusoidal obstructive syndrome (SOS): an overview from the research on adverse drug events and reports (RADAR) project. Leuk Res 2007;31:599–604. [PubMed: 16959316]
11. Arceci RJ, Sande J, Lange B, et al. Safety and efficacy of gemtuzumab ozogamicin in pediatric patients with advanced CD33+ acute myeloid leukemia. Blood 2005;106:1183–1188. [PubMed: 15886328]
12. Bross PF, Beitz J, Chen G, et al. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin Cancer Res 2001;7:1490–1496. [PubMed: 11410481]
13. Petersdorf SH, Kopecky KJ, Slovak M, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood 2013;121:4854–4860. [PubMed: 23591789]
14. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012;379:1508–1516. [PubMed: 22482940]
15. Pautas C, Raffoux E, Lambert J, et al. Outcomes following hematopoietic stem cell transplantation in patients treated with chemotherapy with or without gemtuzumab ozogamicin for acute myeloid leukemia. Blood 2018;132:28–28.
16. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. J Clin Oncol 2014;32:3021–3032. [PubMed: 25092781]
17. Mylotarg (gemtuzumab ozogamicin) [prescribing information]. 2017.
18. Ho VT, Martin AS, Perez WS, et al. 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. Biol Blood Marrow Transplant 2019.
19. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 2009;15:1628–1633. [PubMed: 19896087]
20. Shulman HM, Hinterberger W. Hepatic veno-occlusive disease--liver toxicity syndrome after bone marrow transplantation. Bone Marrow Transplant 1992;10:197–214. [PubMed: 1422475]
21. Jones RJ, Lee KS, Beschorner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation 1987;44:778–783. [PubMed: 3321587]
22. Zhang X, Loberiza FR, Klein JP, Zhang MJ. A SAS macro for estimation of direct adjusted survival curves based on a stratified Cox regression model. Comput Methods Programs Biomed 2007;88:95–101. [PubMed: 17850917]
23. Zhang X, Zhang MJ. SAS macros for estimation of direct adjusted cumulative incidence curves under proportional subdistribution hazards models. Comput Methods Programs Biomed 2011;101:87–93. [PubMed: 20724020]
24. Aplenc R, Alonzo TA, Gerbing RB, et al. Safety and efficacy of gemtuzumab ozogamicin in combination with chemotherapy for pediatric acute myeloid leukemia: a report from the Children's Oncology Group. J Clin Oncol 2008;26:2390–3295. [PubMed: 18467731]
25. Wadleigh M, Richardson PG, Zahrieh D, et al. Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. Blood 2003;102:1578–1582. [PubMed: 12738663]
26. Palmer J, McCune JS, Perales MA, et al. Personalizing busulfan-based conditioning: considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee. Biol Blood Marrow Transplant 2016;22:1915–1925. [PubMed: 27481448]
27. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood 2000;96:4075–4083. [PubMed: 11110676]
28. Sorror ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. J Clin Oncol 2007;25:4246–4254. [PubMed: 17724349]
29. Mylotarg (gemtuzumab ozogamicin) [prescribing information]. 2020.

TABLE 1

Outcomes in all patients

Outcomes[a]	GO-exposed group *n* = 148	Control group *n* = 348
VOD/SOS at 100 days	16 (11–23)	10 (7–13)
Severe VOD/SOS at 100 days	8 (4–13)	3 (2–5)
OS[b]		
100 days	85 (78–90)	87 (83–90)
6 month	78 (71–84)	80 (75–84)
1 year	69 (61–76)	69 (65–74)
3 years	56 (48–63)	57 (52–62)
5 years	51 (43–58)	55 (50–60)
DFS[b]		
1 year	59 (51–66)	62 (57–67)
3 years	47 (39–54)	50 (45–55)
5 years	42 (35–50)	48 (43–53)
Relapse[b]		
1 year	25 (19–32)	27 (23–32)
3 years	35 (28–42)	35 (30–40)
5 years	37 (30–44)	37 (32–41)
NRM[b]		
1 year	13 (8–18)	11 (8–15)
3 years	15 (10–21)	15 (11–19)
5 years	18 (12–24)	15 (12–20)

Values are % (95% CI).

[a]From date of transplant.

[b]Adjusted probability estimates.

CI, confidence interval; DFS, disease-free survival; GO, gemtuzumab ozogamicin; NRM, nonrelapse mortality; OS, overall survival; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome

TABLE 2

Multivariate analysis of outcomes

	VOD/SOS at 100 days		OS		DFS		Relapse		NRM	
Covariates[a]	**OR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
GO exposure										
GO vs. no GO	2.26 (1.31–3.91)	0.004	1.12 (0.85–1.48)	0.43	1.30 (0.88–1.92)	0.20	1.30 (0.78–2.17)	0.32	1.23 (0.66–2.30)	0.51
HCT-specific comorbidity index										
≥3 vs. 0–2	–	–	1.68 (1.20–2.36)	0.003	–	–	–	–	–	–
Cytogenetics[b]										
Intermediate vs. favorable	–	–	2.06 (1.09–3.88)	0.03	–	–	–	–	–	–
Poor vs. favorable	–	–	1.98 (1.04–3.77)	0.04	–	–	–	–	–	–
Disease status										
Relapse/PIF vs. CR1	–	–	2.99 (2.19–4.10)	<0.001	3.11 (1.99–4.84)	<0.001	4.26 (2.36–7.69)	<0.001	–	–
Graft type										
Bone marrow vs. umbilical cord blood	–	–	–	–	–	–	2.46 (1.39–4.35)	0.002	–	–
Peripheral blood vs. umbilical cord blood	–	–	–	–	–	–	2.13 (1.06–4.26)	0.03	–	–
Conditioning regimen										
MAC-chemotherapy, Bu PK vs. MAC-TBI	2.84 (1.49–5.40)	0.002	–	–	–	–	–	–	1.95 (1.05–3.59)	0.03

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

[a]Significant covariates (P <0 .05) reported with the exception of GO exposure, which is reported for all outcomes regardless of significance.

[b]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, mixed lineage leukemia 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)

Bu, busulfan; CI, confidence interval; CR1, first complete remission; DFS, disease-free survival; GO, gemtuzumab ozogamicin; HCT, hematopoietic cell transplantation; HR, hazard ratio; MAC, myeloablative conditioning; NRM, nonrelapse mortality; OR, odds ratio; OS, overall survival; PIF, primary induction failure; PK, pharmacokinetic; TBI, total body irradiation; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome

TABLE 3

Death summary

	GO-exposed group *n* = 148	Control group *n* = 348
Number of deaths	74	158
Cause		
Primary disease	35 (47)	91 (57)
Graft failure	0	1 (<1)
GVHD	4 (5)	9 (6)
Infection	10 (14)	11 (7)
Interstitial pneumonia/ARDS	3 (4)	6 (4)
Organ failure		
VOD/SOS	3 (4)	1 (<1)
Cardiac failure	1 (1)	2 (1)
Pulmonary failure	5 (7)	9 (6)
CNS failure	1 (1)	0
Multiple organ failure	3 (4)	12 (8)
Organ failure, not specified	1 (1)	2 (1)
Secondary malignancy	0	2 (1)
Hemorrhage	3 (4)	5 (3)
Other	3 (4)	4 (3)
Not reported	2 (3)	3 (2)

Values are *n* (%).

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