Supportive Care in Cancer (2024) 32:552
https://doi.org/10.1007/s00520-024-08732-8

RESEARCH

Impact of dexamethasone on transplant-related mortality in pediatric patients: a multi-site, propensity score–weighted, retrospective assessment

Edric Paw Cho Sing[1] · George A. Tomlinson[2] · Tal Schechter[3] · Muhammad Ali[3] · Rachel Phelan[4] · S. Rod Rassekh[5] · Krista McKinnon[6] · Gefen Aldouby Bier[7] · Marianne van de Wetering[8] · Sergio Gomez[9] · Lillian Sung[3,10] · L. Lee Dupuis[10,11]

Received: 13 December 2023 / Accepted: 10 July 2024

Abstract

Dexamethasone use during hematopoietic cell transplant (HCT) conditioning varies between pediatric centers. This study aimed to estimate the difference in 1-year treatment-related mortality (TRM) between patients who did or did not receive dexamethasone during HCT conditioning. Secondary objectives were to estimate the difference between dexamethasone-exposed and dexamethasone-unexposed groups in 1-year event-free survival (EFS), time to neutrophil engraftment, acute graft-versus-host disease (aGVHD), and invasive fungal disease (IFD) at day + 100. This was a seven-site, international, retrospective cohort study. Patients < 18 years old undergoing their first allogeneic or autologous myeloablative HCT for hematologic malignancy or aplastic anemia between January 1, 2012, and July 31, 2017, were included. To control for potential confounders, propensity score weighting was used to calculate the standardized mean difference for all endpoints. Among 242 patients, 140 received dexamethasone during HCT conditioning and 102 did not. TRM was unaffected by dexamethasone exposure (1.7%; 95% CI − 7.4, 10.2%). Between-group differences in secondary outcomes were small. However, dexamethasone exposure significantly increased possible, probable, and proven IFD incidence (9.0%, 95% CI 0.8, 17.3%). TRM is not increased in pediatric patients who receive dexamethasone during HCT conditioning. Clinicians should consider potential IFD risk when selecting chemotherapy-induced vomiting prophylaxis for pediatric HCT patients.

Keywords Treatment-related mortality · Hematopoietic cell transplant · Pediatrics · Dexamethasone · Chemotherapy-induced vomiting

✉ L. Lee Dupuis
lee.dupuis@utoronto.ca

[1] Neonatal and Pediatric Pharmacy, Surrey Memorial Hospital, Surrey, BC, Canada

[2] Department of Medicine, Toronto General Hospital, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada

[3] Division of Haematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada

[4] Division of Hematology and Oncology, Department of Pediatrics, Medical College of Wisconsin, Madison, USA

[5] Division of Pediatric Hematology/Oncology/BMT, Department of Pediatrics, University of British Columbia, Vancouver, Canada

[6] Pharmacy Services, Alberta Children's Hospital, Calgary, AB, Canada

[7] Division of Clinical Pharmacy, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, Hebrew University of Jerusalem and Department of Bone Marrow Transplantation and Cancer Immunotherapy Department, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

[8] Paediatric Oncology Department, Princess Máxima Center for Paediatric Oncology, Utrecht, The Netherlands

[9] Stem Cell Transplantation Unit, Hospital de Niños Sor Maria Ludovica, La Plata, Argentina

[10] Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, 555 University Ave, Toronto, ON M5G 1X8, Canada

[11] Department of Pharmacy, Leslie Dan Faculty of Pharmacy, The Hospital for Sick Children, University of Toronto, Toronto, Canada

Published online: 25 July 2024

Introduction

The conditioning given to prepare pediatric patients for hematopoietic cell transplant (HCT) includes chemotherapy with or without total body irradiation (TBI) and is often highly emetogenic. Almost all children receiving HCT conditioning experience nausea and vomiting despite receiving antiemetic agents [1]. Controlling nausea and vomiting in these children not only improves their quality of life but also may reduce the risk of downstream complications due to malnutrition and gut microbiome disruption [2–5].

Clinical practice guidelines have strongly recommended that adults and children receiving highly emetogenic chemotherapy (HEC) receive an antiemetic regimen that includes dexamethasone [6–9]. The addition of dexamethasone increases the likelihood of completely controlling chemotherapy-induced vomiting (CIV) by twofold in children [10]. Yet, the use of dexamethasone as an antiemetic is highly polarized among pediatric HCT centers [11, 12]. Concerns that dexamethasone may hinder the success of HCT may be a barrier to its use. These concerns typically focus on the risk of treatment-related mortality (TRM). Other concerns include reduced event-free survival (EFS) related to relapse and TRM, delayed neutrophil engraftment, acute graft-versus-host disease (aGVHD), and invasive fungal disease (IFD). There is no direct evidence regarding the impact of dexamethasone exposure during HCT conditioning on TRM.

The primary objective of this study was to estimate the difference in 1-year TRM associated with dexamethasone exposure during HCT conditioning. The secondary objectives were to estimate the differences in 1-year EFS, time to neutrophil engraftment, aGVHD, and IFD associated with dexamethasone exposure during HCT conditioning.

Methods

This was a seven-site, multi-national, retrospective cohort study. Names and locations of the participating sites are presented in Supplementary Table 1. The Research Ethics Board of The Hospital for Sick Children approved the study (# 1000057005) as did the Research Ethics Boards of participating sites. The need for informed consent and assent was waived given the retrospective nature of the study.

Patients

All patients who underwent HCT from January 1, 2012, through July 31, 2017, at participating sites were identified using institutional databases and were screened for study inclusion. Patients were included if they were 18 years of age or younger at day 0 (date of stem cell infusion); diagnosed with acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, non-Hodgkin's lymphoma, chronic myeloid leukemia, or aplastic anemia; received their first allogeneic or single autologous HCT between January 1, 2012, and July 31, 2017; and received myeloablative conditioning.

Patients were excluded if they had Down syndrome or severe combined immune deficiency or if they underwent tandem autologous HCT. They were also excluded if they received corticosteroids other than dexamethasone for chemotherapy-induced nausea and vomiting (CINV) prophylaxis; received physiological supplementation with glucocorticoid agents; received dexamethasone during HCT conditioning for 1 to 71 h; received sirolimus, cyclophosphamide, or corticosteroids for aGVHD prophylaxis; or received, from day 0 to the day of neutrophil engraftment, granulocyte colony stimulating factors (e.g., filgrastim), ganciclovir, or trimethoprim-sulfamethoxazole. Patients who were receiving active treatment for IFD at the time of admission for HCT were also excluded.

Patients were divided into two groups based on dexamethasone exposure. The exposed group had received dexamethasone for at least 3 consecutive days from the start of HCT conditioning through day − 1. Dexamethasone dose and administration route, dates, and times were recorded for this group. The unexposed group received no dexamethasone from the start of HCT conditioning through day − 1.

During the study period, fluconazole (3 sites), posaconazole (1 site), voriconazole (1 site), twice-weekly amphotericin (1 site), caspofungin (3 sites), or micafungin (1 site) was administered for antifungal prophylaxis at participating sites. Note that more than one agent was used during the study period at three sites.

Data collection and definitions

Data were obtained from the health record: patient demographic data (age, diagnosis leading to HCT), HCT characteristics (type of HCT (autologous/allogeneic), date of day 0, HCT conditioning regimen, stem cell source, and, for allogeneic HCT, donor sex and donor type (human leukocyte antigen (HLA)–identical sibling donor, haploidentical, unrelated donor, or other)), CINV prophylaxis administered, and date of neutrophil engraftment. For the first 100 days following HCT, agents given for acute GvHD prophylaxis and, if applicable, presence of aGVHD and grade were tracked. Disease status (early, intermediate, late) was determined as described in the European Group for Blood and Marrow Transplantation (EBMT) risk score [13]. The emetogenicity of the chemotherapy component of HCT conditioning regimens was classified using a pediatric guideline [14]. Total body irradiation was classified as highly emetic [9].

The primary endpoint of this study was the difference in the incidence of TRM at 1 year between the dexamethasone-exposed and dexamethasone-unexposed groups. TRM was defined as death in the absence of recurrence or progression of prior disease for which HCT was indicated within 1-year post-HCT [15].

The secondary endpoints of this study were incidence of 1-year EFS, time to neutrophil engraftment, incidence of aGVHD at day + 100, and IFD at day + 100. EFS was defined as the absence of all of the following: engraftment failure, recurrence or progression of disease for which HCT was indicated, and death. Engraftment failure was defined as the failure to achieve neutrophil engraftment, loss of neutrophil engraftment, or loss of full-donor chimerism for allogeneic HCT. Full-donor chimerism was defined as having donor hematopoiesis ≥ 95%. Receipt of a second unplanned HCT or donor lymphocyte infusion after day 0 because of inadequate hematopoietic function was considered to indicate engraftment failure regardless of ANC values.

Time to neutrophil engraftment was defined as the number of days between day 0 and the first of 3 consecutive days where the absolute neutrophil count (ANC; sum of the neutrophil and band counts) was 0.5×10^9 cells/L or higher. If neutrophil engraftment was not achieved by the end of transplant hospitalization and no further measurements were documented, then time to neutrophil engraftment was deemed to be not evaluable.

aGVHD occurring in the first 100 days following HCT was graded using the modified Glucksberg scale [16].

Presence of proven, probable, or possible IFD in the first 100 days following HCT was categorized by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [17] by the site investigator.

Data analysis

Demographic data (patient and HCT information) were summarized using descriptive statistics.

Propensity score (PS) weighting was used to control for potentially confounding patient- and transplant-related factors. The PS reflects the probability of a patient being exposed to dexamethasone. First, a PS (from 0 to 1) was calculated for each patient from a logistic regression analysis where dexamethasone exposure is the outcome, using five pre-specified covariates suspected to influence administration of dexamethasone and to potentially be related to our outcomes, based on clinical experience:

- EBMT risk score [13] (from 0 to 7)
- Stem cell source (peripheral blood, bone marrow, umbilical cord blood)
- History of documented/suspected IFD prior to the start of conditioning (yes or no)
- Receipt of highly emetogenic conditioning (yes or no)
- Receipt of palonosetron for CINV prophylaxis during HCT (yes or no)

We used the resultant PS to calculate inverse probability of treatment weights (IPTW) that allow estimation of the average treatment effect; this is the effect of assigning all patients, versus no patients, to receive dexamethasone. These weights are used to construct weighted samples. These weighted samples were first used to check the balance in baseline covariates in the dexamethasone-exposed and dexamethasone-unexposed samples. The standardized mean difference (SMD) was calculated for each covariate; values of the SMD < 0.1 are generally considered to indicate that good balance has been achieved. Once balance was demonstrated on the variables above, the weighted samples were used to estimate differences between primary and secondary outcomes. The bootstrap method was used to compute 95% confidence intervals for all estimates; in each of 2000 resamples of the entire dataset, the propensity score and average treatment effect for each outcome were recalculated.

For analysis of IFD and aGVHD, patients were counted as not having events if they experienced the following competing events prior to day + 100 and were not known to have experienced the event of interest: death, disease relapse or recurrence, and second HCT. The occurrence of these events was recorded as a binary outcome, not the time of their occurrence. For time to neutrophil engraftment, patients were censored if they experienced any of the competing events listed above prior to neutrophil engraftment.

After reviewing the table of balance on the baseline covariates, a sensitivity analysis was run. Diagnosis and calendar year were included in the PS calculation (as they were related to dexamethasone use), and patients were excluded if they were treated with palonosetron (as this precluded use of dexamethasone) or if they had a diagnosis of "other" (as patient number was low). All analyses were run in R version 4.3.2.

Results

The seven participating sites contributed data for 242 eligible patients: 140 in the exposed group and 102 in the unexposed group. Two sites, contributing a total of 33 patients, never gave dexamethasone; one site, contributing 20 patients, gave dexamethasone to only one patient. Dexamethasone use was variable at the remaining four sites. Data for recurrence, mortality, and TRM was missing for one patient; this patient was excluded for all analyses of

these outcomes. Data for recurrence was missing for another patient who was therefore excluded from analysis of EFS.

Most patients underwent allogeneic HCT (98%), had a diagnosis of leukemia (83%), and received highly emetogenic, multi-day conditioning (99%). Patients in the exposed group received dexamethasone for 3 to 12 days (median 7 days). Median cumulative dexamethasone dose during conditioning was 71.1 mg (range 11 to 248.5 mg). The median cumulative dexamethasone dose was able to be calculated based on body surface area for 106 patients and was 95.2 mg/m^2 (range 13.4 to 186.7 mg/m^2). Patient and HCT characteristics are summarized in Table 1.

Propensity score determination

Summaries of the baseline variables are summarized in Table 1 for the entire unweighted sample and the IPTW-weighted sample. Several variables potentially related to the study outcomes (diagnosis, stage, EBMT score) were unbalanced at baseline. After IPTW weighting, balance was excellent for most variables (with all SMDs near zero), except for receipt of palonosetron, because no patient who received this treatment also received dexamethasone, and two diagnosis categories. In the sensitivity analysis with the revised PS, balance was improved further (Supplementary Table 2).

Outcomes

Unadjusted and adjusted analyses of primary and secondary outcomes are presented in Table 2. The observed incidence of TRM was 7.1% (10/140) and 4.9% (5/101) in the exposed and unexposed groups, respectively. In both the unadjusted and adjusted comparisons, dexamethasone use was associated with very wide confidence intervals, with the IPTW-adjusted difference in TRM being 1.7% (95% CI − 7.4, 10.2%; $p = 0.704$).

Three patients (exposed group: 0; unexposed group: 3, 2.9%) experienced engraftment failure. Recurrence or relapse of the condition for which patients underwent HCT occurred in 67 patients (exposed group: 38/140, 27.1%; unexposed group: 31/102. 30.4%). Approximately one-quarter of patients (exposed group: 34/140, 24.3%; unexposed group: 24/102, 23.5%) died within 1 year of HCT. The 1-year EFS was 65.7% (92/140) and 63.0% (63/100) in the exposed and non-exposed groups, respectively, with an IPTW-adjusted difference of 2.5% (95% CI − 13.4, 17.4%; $p = 0.756$). The IPTW-adjusted differences in time to neutrophil engraftment and aGVHD were similarly not significant.

The proportion of patients with possible, probable, or proven IFD at day + 100 was significantly larger in the exposed group (16.8%, 23/137) compared to the unexposed group (7.0%, 7/100) in the IPTW-adjusted analysis (9.0% difference; 95% CI 0.8, 17.3%; $p = 0.028$). There were five cases of proven (exposed group: 3; unexposed group: 2), three cases of probable (exposed group: 2; unexposed group: 1), and 22 cases of possible IFD (exposed group: 18; unexposed group: 4). Of these, four patients had TRM at 1 year: two with proven IFD (exposed group: 1; unexposed group: 1) and two with possible IFD (exposed group: 1; unexposed group: 1).

The results of the post hoc sensitivity analysis (Supplementary Table 3) were similar to the main analysis except that the between-group difference in IFD was no longer statistically significant (10% difference; 95% CI − 1.3, 20.8; $p = 0.078$).

Discussion

In this retrospective study of pediatric patients, we observed no statistically significant associations between receipt of dexamethasone during HCT conditioning and 1-year TRM, 1-year EFS, time to neutrophil engraftment, or aGVHD. Yet, effects were uncertain since the 95% CIs were wide, encompassing the possibility of both clinically important benefits and harms. The rate of possible, probable, or proven IFD was, however, significantly higher in the exposed group.

Factors associated with mortality following HCT are captured in the EBMT risk score: age, disease status, time period between diagnosis to HCT, donor type, and, for allogeneic HCT, donor recipient sex combination. Other predictive models have been proposed but no model outperforms others with respect to predictive capacity [18], and no model incorporates receipt of corticosteroid as a risk factor for TRM.

In the adjusted analysis, we found that dexamethasone receipt during HCT conditioning was associated with IFD. This might be a direct association with dexamethasone [19–21] or related to residual confounding. It is notable that the preponderance of IFD cases in our cohort was possible cases (22/30) rather than probable or proven cases. However, others have also identified corticosteroid use as a significant predictor of invasive fungal infection in pediatric allogeneic HCT recipients [22–24]. Hovi et al. report a significantly higher incidence of invasive fungal infections in pediatric patients who received high-dose followed by conventional-dose methylprednisolone (0.25 to 1 g/day for 5 days followed by conventional-dose prednisone 2 mg/kg/day) compared to patients who received conventional-dose prednisone or no corticosteroids [24]. Dvorak et al. reported an increased risk of invasive fungal infections among pediatric allogeneic HCT recipients who received corticosteroids (type and timing with respect to HCT undefined) 2 mg/kg/day or more for at least 10 days [22]. Lastly, Hol et al. report that the

Table 1 Characteristics of patients who did or did not receive dexamethasone during conditioning and their hematopoietic cell transplants.

		Unweighted			Propensity Score Weighted		
	All patients (*N*=242)	Dexamethasone-Exposed (*N*=140)	Dexamethasone-Unexposed (*N*=102)	SMD	Dexamethasone-Exposed	Dexamethasone-Unexposed	SMD
Propensity Score Components							
EBMT Risk Score (mean, SD)	1.83 (1.2)	1.99 (1.3)	1.63 (1.2)	0.29	1.82 (1.2)	1.84 (1.2)	0.02
History of documented/suspected IFD (*N* (%))	26 (10.7)	14 (10.0)	12 (11.8)	0.06	10%	10%	0.02
Receipt of Highly Emetic	239 (99)	140 (100)	99 (97)	0.25	100%	99%	0.17
Conditioning (*N* (%))							
Total body irradiation	122 (50)	70 (50.0)	52 (51)	0.02	49%	47%	0.04
Highly emetic chemotherapy	226 (93)	136 (97)	90 (88)	0.35	95%	94%	0.07
Stem Cell Source (*N* (%))							
Bone Marrow	156 (65)	93 (66)	63 (62)	0.10	63%	64%	0.02
Peripheral Blood	51 (21)	19 (14)	32 (31)	0.44	22%	21%	0.04
Umbilical Cord Blood	35 (15)	28 (20)	7 (7)	0.39	15%	16%	0.02
Receipt of Palonosetron for CINV Prophylaxis (*N* (%))	6 (2.5)	0	6 (5.9)	0.35	0	4%	0.30
Other Patient Characteristics							
Males (*N* (%))	142 (59)	83 (59)	59 (58)	0.03	58%	61%	0.04
Age at HCT, years (mean; SD)	9.6 (5.1)	9.6 (4.9)	9.5 (5.3)	0.01	10.2 (4.7)	9.1 (5.3)	0.22
Diagnosis (*N* (%))							
Acute lymphoblastic leukemia	103 (43)	60 (43)	43 (42)	0.01	42%	38%	0.10
Acute myelogenous leukemia	97 (40)	49 (35)	48 (47)	0.25	34%	50%	0.33
Myelodysplastic syndrome	21 (9)	16 (11)	5 (5)	0.24	13%	5%	0.30
Non-Hodgkin lymphoma	13 (5)	10 (7)	3 (3)	0.19	7%	5%	0.07
Other	8 (3)	5 (4)	3 (3)	0.04	4%	2%	0.07
Disease Stage (*N* (%))							
Early	121 (50)	62 (45)	59 (58)	0.26	52%	50%	0.03
Intermediate	95 (39)	58 (41)	37 (36)	0.11	36%	45%	0.19
Late	25 (10)	19 (14)	6 (6)	0.26	13%	5%	0.29
Missing	1	1	0				
Other HCT Characteristics							
Mean Conditioning Duration, days (SD)	5.7 (1.6)	6.0 (1.5)	5.4 (1.7)	0.38	5.9 (1.6)	5.6 (1.7)	0.18
Type of HCT (*N* (%))							
Allogeneic	237 (98)	137 (98)	100 (98)	0.01	97%	99%	0.10
Autologous	5 (2)	3 (2)	2 (2)				
If allogeneic:							
Donor type (*N* (%))							
HLA-identical sibling	86 (36)	45 (33)	41 (40)	0.17	33%	35%	0.05
Haploidentical	9 (3.8)	6 (4.4)	3 (3.0)	0.07	5%	3%	0.14
Matched unrelated	131 (54)	82 (59)	49 (48)	0.21	57%	55%	0.04
Other	11 (4.6)	4 (3)	7 (7)	0.15	5%	7%	0.11
Recipient-donor sex mismatch (*N* (% of allogeneic))							
Male recipient – Female donor	55 (23.2)	32 (23.4)	23 (23.0)	0.01			
Female recipient – Male donor	55 (23.2)	33 (24.1)	22 (22.0)	0.05			

N number, *SD* standard deviation, *EBMT* European Group for Blood and Marrow transplantation, *HCT* hematopoietic cell transplant, *HLA* human leukocyte antigens, *SMD* standardized mean difference. Note: Propensity Score -weighted SMDs are not presented for the subsamples with allogeneic mismatch type

Table 2 Primary and secondary study endpoints: unadjusted and adjusted by inverse probability of treatment weighting

Outcome	Outcomes in the entire sample*		Unadjusted difference (%, 95% CI) *p* value	IPTW-adjusted difference** (%, 95% CI) *p* value
	Dexamethasone- exposed	Dexamethasone-unexposed		
Treatment-related mortality (proportion, %)	10/140 (7.1)	5/101 (4.9)	2.2 (−4.7 to 9.1) $p=0.671$	1.7 (−7.4 to 10.2) $p=0.704$
1-year event-free survival (proportion, %)	92/140 (65.7)	63/100 (63.0)	2.7 (−10.4 to 15.9) $p=0.767$	2.5 (−13.4 to 17.4) $p=0.756$
Days to neutrophil engraftment (median (IQR))	22 (17–27)	18.5 (15–24)	3.5 (1–6) $p=0.004$	1.5 (−2.4, 3.0) $p=0.747$
aGVHD Grade ≥ 1 (vs grade 0) (proportion, %)	77/137 (56.2)	44/97 (45.4)	10.8 (−3 to 24.7) $p=0.133$	7.2 (−7.4 to 21.3) $p=0.342$
Proven, probable, possible invasive fungal disease (proportion, %)	23/137 (16.8)	7/100 (7.0)	9.8 (0.9 to 18.7) $p=0.041$	9.0 (0.8 to 17.3) $p=0.028$

N number, *CI* 95% confidence interval, *IPTW* inverse probability of treatment weighting, *aGVHD* acute graft-versus-host disease

*Denominators reflect missing or censored data

**95% CI from bootstrap

use of high-dose corticosteroids (dose and type undefined) post-HCT was significantly associated with the incidence of invasive fungal infection [23].

Prolonged receipt of corticosteroids (mean minimum dose of 0.3 mg/kg/day (prednisone equivalent) for at least 3 weeks prior to HCT) is incorporated into the current EORTC definitions of probable IFD as a host factor [17, 25]. This mean minimum prednisone dose corresponds to a dexamethasone dose of 0.045 mg/kg/day. Our analysis, however, suggests that even a relatively brief duration of dexamethasone exposure may have an important impact on IFD incidence.

For patients receiving HEC, the addition of dexamethasone to a serotonin-3 receptor antagonist increases the likelihood of experiencing acute phase complete vomiting control by 29% and the likelihood of complete nausea control by 46% [26]. Thus, when weighing the risks and benefits of using dexamethasone as an antiemetic during HCT conditioning for individual patients, the risk of IFD must be balanced against the increased risk of uncontrolled CINV when dexamethasone is not administered. Clinicians may consider omitting dexamethasone for initial CINV prophylaxis in patients at high risk of IFD [27]. When dexamethasone is used, the lowest possible effective dose should be administered for the shortest possible length of time [28]. It has been suggested that antiemetic selection decisions for HCT patients be taken daily depending on the emetogenicity of the HCT conditioning to be given and the patient's degree of CINV control [29]. In any case, clinical practice guideline–consistent CINV prophylaxis, with or without dexamethasone, should be administered during HCT conditioning [30, 31]. Clinical practice guideline–consistent options include the use of palonosetron over other serotonin-3 receptor antagonists and the addition of aprepitant, fosaprepitant, or olanzapine.

The most significant limitations of this study are a result of its retrospective design. That is, the integrity of our data is dependent on the quality of documentation in the health record. It is possible that the choice to administer or omit dexamethasone for CINV prophylaxis was based on individual patient or site factors that were not accounted for in our analysis. For example, reports of IFD, particularly possible IFD, may reflect site practices for investigation of persistent fever in HCT patients. It is also important to realize that our cohort was historical and that approaches to antifungal prophylaxis and diagnostics have improved over time. For example, patients in this study received antifungal prophylaxis but some did not receive antimold prophylaxis, a practice that is now strongly recommended to reduce the risk of IFD and IFD-related mortality [27]. It is possible that receipt of antimold prophylaxis may mitigate the impact of dexamethasone on the risk of IFD. The study is also limited as we did not collect data on parenteral nutrition use and duration of hospitalization; dexamethasone administration may influence these outcomes [1]. Lastly, we are unable to comment on the association between dexamethasone use for less than 3 consecutive days on TRM and other transplant outcomes. The participation of geographically dispersed sites representing four continents is a strength of this study as is the use of propensity weighting to balance potential confounding factors and an accepted TRM risk score in the calculation of the PS.

Our findings indicate that TRM risk is not increased in patients who receive dexamethasone for 3 consecutive days or more during HCT conditioning. Further, EFS, time to neutrophil engraftment, and, among patients undergoing allogeneic HCT, aGVHD are unlikely to be affected by dexamethasone use immediately prior to HCT. However, we observed substantial uncertainty in all endpoint estimates. Nevertheless, this information will allow clinicians to better weigh the

benefits that dexamethasone offers with respect to improved CINV control against the potential risk of possible, probable, or proven IFD in individual patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-024-08732-8.

Acknowledgements We are grateful to Drs. Martin Offringa and Andrew Willan for initial guidance regarding statistical methods. We thank Alysha Wong, Caleb Rans, Esther Vincke, Sahiba Khurana, and Vivek Gill for their assistance with data retrieval. We are also grateful to Navpreet Kaur for administrative assistance.

Author contribution EPCS contributed to study conception and design, collected data, analyzed the data, interpreted the data, and took a primary role in writing the first draft of the manuscript.

GAT created the statistical plan, analyzed the data, and contributed to writing the first draft of the manuscript.

TS contributed to study conception and design, interpreted the data, and participated in manuscript revision.

MA contributed to study conception and design, interpreted the data, and participated in manuscript revision.

RP contributed to study conception and design, collected data, interpreted the data, and participated in manuscript revision.

SRR contributed to study conception and design, oversaw data collection, interpreted the data, and participated in manuscript revision.

KM contributed to study conception and design, collected data, interpreted the data, and participated in manuscript revision.

GAB contributed to study conception and design, collected data, interpreted the data, and participated in manuscript revision.

MvdW contributed to study conception and design, oversaw data collection, interpreted the data, and participated in manuscript revision.

SG contributed to study conception and design, oversaw data collection, interpreted the data, and participated in manuscript revision.

LS contributed to study conception and design, interpreted the data, and took a primary role in writing the first draft of the manuscript.

LLD led the study conception and design, coordinated and curated data, analyzed the data, interpreted the data, took a primary role in writing the first draft of the manuscript, and coordinated revisions.

Funding This research was supported by a research grant from the Canadian Society of Hospital Pharmacists Foundation.

Data availability The datasets generated during and/or analyzed during the current study are not publicly available as per the limitations placed by institutional Research Ethics Boards but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The Research Ethics Board of The Hospital for Sick Children, Canada, approved the study (# 1000057005) as did the Research Ethics Boards of participating sites (see Supplementary Table 1). The REB of The Hospital for Sick Children operates in compliance with the Tri-Council Policy Statement, ICH Guideline for Good Clinical Practice E6(R1), Ontario Personal Health Information Protection Act (2004), Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations, and the Medical Devices Regulations of Health Canada. The need for informed consent and assent was waived given the retrospective nature of the study.

Competing interests L. Lee Dupuis is a Deputy Associate Editor of Supportive Care in Cancer. No other author has a relevant non-financial interest to disclose.

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