1559

IDWeek 2018

SAN FRANCISCO, CALIFORNIA
October 3-7, 2018

HEMATOPOIETIC CELL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE: IMPACT OF DONOR TYPE ON PRE-ENGRAFTMENT BLOOD STREAM INFECTIONS

Chiara Oltolini[1], Raffaella Greco[2], Laura Galli[1], Francesca Lorentino[2], Elisabetta Xue[2], Maria Teresa Lupo Stanghellini[2], Daniela Clerici[2], Fabio Giglio[2], Jacopo Peccatori[2], Massimo Bernardi[2], Consuelo Corti[2], Paolo Scarpellini[1], Antonella Castagna[3], Fabio Ciceri[2-3]

1 Clinic of Infectious Diseases, Division of Immunology, IRCCS San Raffaele, Milan, Italy; 2 Hematology and Bone Marrow Transplantation, IRCCS San Raffaele, Milan, Italy; 3 Università Vita-Salute San Raffaele

Contact Informations:

Chiara Oltolini, MD
Clinic of Infectious Diseases,
Division of Immunology
IRCCS San Raffaele, Milan, Italy
Phone number: +390226439195
Fax number: +390226437903
E-mail: oltolini.chiara@hsr.it

Abstract

Background : the aim of the study was to estimate the cumulative incidence of pre-engraftment blood stream infections (PE-BSI), its predictive factors and the infection-related mortality (IRM) after hematopoietic cell transplantation (HCT) from any donor type, with post-transplant cyclophosphamide (PTCY).

Methods: retrospective cohort study on 235 adults who underwent peripheral blood HCT from every donor type with PTCY platform, from 2013 to 2017 at San Raffaele Scientific Institute. The Poisson regression was used to estimate the crude incidence rate (IR) of PE-BSI. The Fine-Gray competing risk model was applied to estimate the cumulative incidence function (CIF) of the first PE-BSI and its predictive factors and of IRM.

Results : patients' characteristics are reported in Table 1. During 5316 person-days of follow-up (PDFU), 77 PE-BSI episodes occurred in 72 patients: IR=1.45 per 100-PDFU [95% confidence interval (95%CI) 1.13-1.77]. The median time to PE-BSI was 13 days (IQR: 7-17) and the estimated CIF at 28 days was 32% (95%CI: 26%-39%); no differences in CIF according to donor type [30% vs 34% vs 32% in match-related, match-unrelated and haploidentical donor, respectively; Gray's test: p=0.968]. Among the 87 isolated pathogens, 60% were Gram-positive bacteria (GPB), 39% Gram-negative bacteria (GNB) and 1% non-tuberculous mycobacteria. CIFs of GNB and GPB PE-BSI by type of donor are shown in Figure 1. By multivariate analysis (Table 2), after adjustment for age, sex, year of HCT, donor type and disease phase at HCT, the CIF of any PE-BSI was higher in subjects with absolute neutrophils count ≤500 for ≥7 days before HCT [adjusted hazard ratio (AHR)=2.90] and in multi-drug resistant (MDR) GNB rectal carriers before HCT [AHR=2.68]. These covariates were confirmed as independent factors also for GNB PE-BSI. Overall, IRM at 30 days was 5% (95%CI: 2%-8%) with no differences by donor type (Gray's test: p=0.106).

Conclusions: HCT with PTCY platform showed a 32% of cumulative incidence of PE-BSI at 28 days and donor type did not affect its occurrence, which was conversely increased by prolonged and severe neutropenia and MDR GNB rectal carriage before HCT. Haploidentical setting did not retain a higher IRM at 30 days than match-related and match-unrelated donors.

Introduction

- Bloodstream infections (BSI) are an important complication in allogenic hematopoietic cell transplantation (HCT) recipients, particularly during pre-engraftment neutropenia. BSI affects from 16% to 40% patients, with an associated mortality ranging from <5% in case of Gram-positive bacteria (GPB), to up to 64% and 75% in carbapenem-resistant *K. pneumoniae* and *P. aeruginosa* BSI
- Recent studies identified donor type (haploidentical, cord blood transplant), older age and duration of severe neutropenia as risk factors for Gram-negative bacteria (GNB) pre-engraftment BSI (PE-BSI)
- Haploidentical HCT with high-dose post-transplant cyclophosphamide (PTCY) represents a valid alternative for hematological patients who don't have a HLA-identical sibling; recently, PTCY platform has also been applied to HLA-identical siblings and match-unrelated donor (MUD) HCT
- As the incidence and outcomes of infections associated with PTCY platform in adult patients receiving allogenic HCT from any type of donor remains to be determined, we sought to estimate the cumulative incidence of PE-BSI and its predictive factors; we also analyzed the BSI-attributable mortality and the infection-related mortality (IRM).

Methods

We performed a retrospective cohort study on 235 adults who underwent peripheral blood allogenic HCT from every donor type with PTCY platform, from 2013 to 2017 at San Raffaele Scientific Institute.

Patients' follow-up accrued from HCT (day 0) until death, further HCT if necessary for relapsing hematological disease or last visit, whichever occurred first.

PE-BSI definition: isolation of a bacterial or fungal pathogen from ≥1 blood culture of a neutropenic patient since the beginning of conditioning regimen to engraftment. Engraftment was defined as the first of 3 consecutive days of an absolute neutrophils count (ANC) ≥5 x 10^9/L. In case of common skin contaminants, BSI was diagnosed if at least 2 consecutive blood cultures were positive for the same species.

PTCY platform: myeloablative conditioning consisted of treosulfan (14 g/m^2/day) on days -6 to -4, fludarabine (30 mg/m^2/day) on days -6 to -2, and melphalan (70 mg/m^2/day) on days -3 and -2, followed by T cell replete peripheral blood stem cells. Post-grafting immunosuppression consisted of PTCY (50 mg/kg/day) on days 3 and 4, followed by mycophenolate mofetil (MMF, 10mg/kg three times daily) and sirolimus. In the absence of graft versus host disease (GVHD) or disease relapse, tapering of MMF was initiated after engraftment, starting from day 20 to achieve discontinuation by day 30. In case of HCT from HLA-identical sibling MMF was not administered.

IRM definition: IRM was defined as the time from transplant to death by an infectious cause, without relapse/recurrence or GVHD. Deaths from any cause without prior progression are events. Events related to the disease such as relapse/progression or to non-infectious causes of transplant-related mortality (TRM) such as GVHD are competing events.

BSI-attributable mortality definition: in the subgroup of patients with PE-BSI, mortality at day 7 post-BSI (day 0 as the day of the positive blood culture) was recorded; for this analysis of survival after each BSI episode, only single-species GNB and single-species GPB PE-BSI were analyzed to better define etiology impact on early BSI-attributable mortality.

The Poisson regression was used to estimate the crude incidence rate (IR) of PE-BSI. The Fine-Gray competing risk model was applied to estimate the cumulative incidence function (CIF) of the first PE-BSI and its predictive factors and the CIF of IRM.

Table 1 – Baseline and follow-up characteristics of patients who underwent hematopoietic cell transpant with PTCY platform (all patients received antibiotic prophylaxis with levofloxacin)

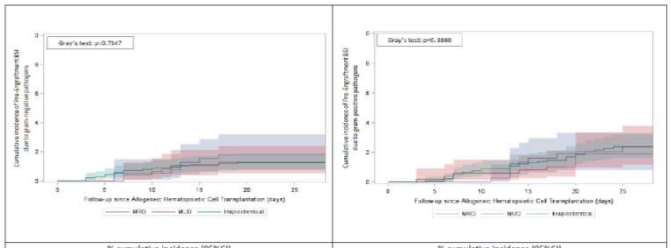
Patients' Characteristics	Overall (n =235)	MRD (n =40)	MUD (n =50)	haplo (n =145)	p-value
BASELINE					
Age at HCT, yr, median (IQR)	49.6 (37.0-62.0)	48.1 (40.9-59.4)	50.6 (37.4-57.0)	51.6 (36.4-63.1)	0.863
Male gender, n (%)	147 (63%)	25 (63%)	33 (66%)	89 (62%)	0.844
Year of HCT, n (%)	2016 (2014-2017)	2016 (2015-2017)	2016 (2016-2017)	2015 (2014-2016)	**<0.0001**
2013-2015	109 (46%)	15 (38%)	9 (18%)	85 (59%)	<0.0001
2016-2017	126 (54%)	25 (62%)	41 (82%)	60 (41%)	
ANC ≤500 for ≥7 days before HCT	66 (28%)	10 (25%)	5 (10%)	51 (35%)	**0.003**
Diagnosis§, n (%)					0.260
Acute myeloproliferative diseases	157 (67%)	27 (68%)	29 (58%)	101 (70%)	
Acute and chronic lymphoproliferative diseases	65 (27%)	11 (27%)	15 (30%)	39 (27%)	
Chronic myeloproliferative diseases	12 (5%)	2 (5%)	5 (10%)	5 (3%)	
Benign/immune-mediated diseases	1 (1%)	0	1 (2%)	0	
Disease phase at HCT, n (%)					**0.001**
>CR1	40 (17%)	1 (2)	9 (18%)	30 (21%)	
CR1	63 (27%)	16 (40%)	20 (40%)	27 (19%)	
Active disease	131 (55%)	23 (58%)	20 (40%)	88 (61%)	
Not applicable	1 (1%)	0	1 (2%)	0	
Conditioning regimen, n (%)					0.286
Myeloablative conditioning	184 (78%)	35 (88%)	39 (78%)	110 (76%)	
Reduced intensity conditioning	51 (22%)	5 (12%)	11 (22%)	35 (24%)	
MDR-GNB rectal carrier within 30 days before HCT, n (%)	18 (8%)	3 (8%)	1 (2%)	14 (10%)	0.214
Number of HCT, n (%)					**0.001**
First allogenic HCT	201 (87%)	39 (98%)	50 (100%)	115 (79%)	
Second allogenic HCT	27 (12%)	1 (2%)	0	26 (18%)	
Third allogenic HCT	4 (3%)	0	0	4 (3%)	
GVHD prophylaxis*					0.387
PT-Cy/sirolimus/(MMF)	231	40 (100%)	50 (100%)	141 (98%)	
PT-Cy/cyclosporine A/MMF	3	0	0	3 (2%)	
FOLLOW-UP					
Follow-up, days, median (IQR)	276 (137-580)	289 (197-577)	316 (174-531)	259 (114-618)	0.579
ANC engraftment, n (%)	225 (96%)	39 (98%)	50 (100%)	136 (94%)	0.144
Time to engraftment, days, median (IQR)	20 (17-24)	20 (16-24)	22 (19-29)	19 (17-24)	**0.046**
Acute GVHD, n (%)	137 (58%)	14 (35%)	27 (54%)	96 (66%)	**0.002**
Acute GVHD grade ≥2, n (%)	76/235 (32%)	6/40 (15%)	12/50 (24%)	58/145 (40%)	0.250
Time to GVHD among subjects who developed aGVHD, days, median (IQR)	24 (15-41)	38 (28-47)	25 (20-44)	21 (14-35)	0.061
PE-BSI, n (%)					
none	164 (70%)	28 (70%)	34 (68%)	102 (70%)	
Single BSI episode	72 (31%)	12 (30%)	16 (32%)	44 (30%)	**0.972**
Two BSI episodes	5 (2%)	0	1 (2%)	4 (3%)	0.563
At least 1 BSI due to Gram-positive bacteria, n (%)	46 (20%)	7 (18%)	10 (20%)	29 (20%)	0.936
At least 1 BSI due to Gram-negative bacteria, n (%)	30 (13%)	7 (18%)	6 (12%)	17 (12%)	0.615
Time to the first BSI after HCT among subjects who developed ≥1 BSI, days, median (IQR)	13 (7-17)	13 (12-15)	13 (7-20)	10 (7-18)	0.549
Antimicrobial resistance score, n (%)					0.051
Susceptible to 1st line antibiotic therapy (PTZ)	13 (18%)	1 (8%)	7 (44%)	5 (11%)	
Susceptible to 2nd line antibiotic therapy (MEM,VAN)	49 (68%)	9 (75%)	8 (50%)	32 (73%)	
Resistant to 2nd line antibiotic therapy (MEM,VAN)	10 (14%)	2 (17%)	1 (6%)	7 (16%)	
Septic shock, n (%)	12 (17%)	2 (17%)	2 (17%)	8 (18%)	0.873
Relapse, n (%)	64 (27%)	13 (33%)	7 (14%)	44 (30%)	0.058
Time to relapse among subjects who had relapse, days, median (IQR)	120 (63-202)	97 (63-129)	102 (73-282)	136 (63-214)	0.540

Abbreviations: HCT, hematopoietic cell transplantation; MRD, match-related donor; MUD, match-unrelated donor; haplo, haploidentical donor; ANC, absolute neutrophils count; CR, complete response; MDR-GNB, multi-drug resistant Gram-negative bacteria; GVHD, graft-versus host disease; PT-Cy, post-transplant cyclophosphamide; MMF, mofetil mycophenolate; PE-BSI, pre-engraftment blood-stream infection; PTZ, piperacillin/tazobactam; MEM, meropenem; VAN, vancomycin.

§ Acute myeloproliferative diseases: acute myeloid leukemia, myelodysplastic syndrome; Acute and chronic lymphoproliferative diseases: acute lymphoblastic leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma; Chronic myeloproliferative diseases: chronic myelogenous leukemia, idiopathic myelofibrosis, myeloproliferative neoplasm; Benign/immune-mediated diseases: chronic granulomatous disease.

* 1 patient died because of ESBL-producing *Escherichia coli* BSI before receiving GVHD prophylaxis

Figure 1 – Cumulative incidence function (CIF) of the first pre-engraftment BSI due to Gram-negative and Gram-positive bacteria according to the type of donor [CIF estimated according to the Fine-Gray method, with engraftment, pre-engraftment death and second HCT as competing events]



	% cumulative incidence (95%CI)				% cumulative incidence (95%CI)			
	MRD	MUD	Haploidentical		MRD	MUD	Haploidentical	
7 days	5% (0.9% - 15.0%)	4.2% (0.8% - 12.7%)	7.2% (3.7% - 12.3%)	7 days	0%	6% (1.5% - 15.0%)	5.2% (2.3% - 9.9%)	
14 days	12.7% (4.6% - 25.2%)	10.6% (3.8% - 21.3%)	11.1% (6.5% - 17.1%)	14 days	13.5% (4.8% - 26.5%)	8.2% (2.6% - 18.2%)	12.2% (7.3% - 18.5%)	
21 days	18.3% (7.9% - 32.0%)	12.7% (5.1% - 24.0%)	12.7% (7.7% - 19.1%)	21 days	19.1% (8.2% - 33.2%)	20.4% (9.9% - 33.6%)	20.5% (13.9% - 28.0%)	
28 days	18.3% (7.9% - 32.0%)	12.7% (5.1% - 24.0%)	12.7% (7.7% - 19.1%)	28 days	19.1% (8.2% - 33.2%)	23.7% (11.9% - 37.8%)	23.8% (16.5% - 31.8%)	

Table 2 – Multivariate Fine-Gray models to assess baseline factors associated with the incidence of any or Gram-negative bacteria (GNB) pre-engraftment BSI (PE-BSI)

Characteristic at HCT	Risk categories	Adjusted HR of any PE-BSI (95%CI)	p-value	Adjusted HR of GNB PE-BSI (95%CI)	p-value
Age	per 3-years older	1.010 (0.959-1.063)	0.716	0.943 (0.866-1.027)	0.178
	>50 vs ≤50 years				
Gender	Female vs Male	0.877 (0.524-1.467)	0.616	0.767 (0.340-1.730)	0.523
Year of HCT	per 2 more recent years	0.942 (0.628-1.411)	0.770	1.024 (0.515-2.036)	0.947
	>2015 vs ≤2015				
ANC ≤500 for ≥7 days before HCT	Yes vs No	2.895 (1.542-5.435)	**0.0009**	4.866 (1.992-11.89)	**0.0005**
MDR-GNB rectal carrier within 30 days before HCT	Yes vs No	2.683 (1.253-5.749)	**0.011**	3.885 (1.288-11.72)	**0.016**
Type of donor			0.496		0.367
	Haploidentical vs MRD	0.929 (0.480-1.801)	0.828	0.656 (0.255-1.688)	0.382
	MUD vs MRD	1.493 (0.758-2.944)	0.387	1.307 (0.417-4.099)	0.646
Disease phase					
	Active disease vs >CR1/CR1	0.886 (0.483-1.624)	0.694	1.074 (0.432-2.674)	0.877

Abbreviations: HCT, hematopoietic cell transplantation; MRD, match-related donor; MUD, match-unrelated donor; haplo, haploidentical donor; ANC, absolute neutrophils count; CR, complete response; MDR-GNB, multi-drug resistant Gram-negative bacteria; PE-BSI, pre-engraftment blood-stream infection.

The multivariate model considered engraftment and pre-engraftment death as competing events; it was constructed by considering the main exposure of interest (type of donor), *a priori* factors known to have a potential effect on the incidence of PE-BSI (age and sex) and other covariates with a p-value<0.2 at univariate analysis.

Results

Overall, 235 HCT recipients were included; 145 patients received haploidentical transplant, while 40 and 50 underwent HLA-identical sibling [match-related donor (MRD)] and MUD transplant, respectively. Patients' characteristics are reported in **Table 1**.

During 5316 person-days of follow-up (PDFU), 77 PE-BSI episodes occurred in 72 patients: IR=1.45 per 100-PDFU [95% confidence interval (95%CI) 1.13-1.77]. The median time to PE-BSI was 13 days (IQR: 7-17) and the estimated CIF at 28 days was 32% (95%CI: 26%-39%); no differences in CIF according to donor type [30% vs 34% vs 32% in MRD, MUD and haploidentical donor, respectively; Gray's test: p=0.968].

Among the 87 isolated pathogens, 60% were Gram-positive bacteria (GPB), 39% Gram-negative bacteria (GNB) and 1% non-tuberculous mycobacteria. CIFs of GNB and GPB PE-BSI by type of donor are shown in **Figure 1**. Among GNB, the most represented pathogens were *Escherichia coli* (18 isolates, 56% ESBL-producers) and *Klebsiella pneumoniae* (9 isolates, 89% KPC-producers).

Mortality at day 7 after 27 single species GNB PE-BSI episodes and 39 single species GPB PE-BSI episodes was 7% (2/27) and 0% (0/39), respectively; while mortality at day 7 after 8 KPC-*K. pneumoniae* PE-BSI episodes was 13% (1/8).

By multivariate analysis (**Table 2**), after adjustment for age, sex, year of HCT, donor type and disease phase at HCT, the CIF of any PE-BSI was higher in subjects with ANC ≤500 for ≥7 days before HCT [adjusted hazard ratio (AHR)=2.90] and in multi-drug resistant (MDR) GNB rectal carriers before HCT [AHR=2.68]. These covariates were confirmed as independent factors also for GNB PE-BSI.

Overall, IRM at 30 days was 5% (95%CI: 2%-8%) with no differences by donor type (Gray's test: p=0.106). IRM at 30 days among transplant recipients who developed GNB PE-BSI and GPB PE-BSI was 17% (95%CI: 5%-34%) and 8% (95%CI: 2%-18%),respectively; while patients who did not develop any PE-BSI had a 30-days IRM of 2% (95%CI: 1%-5%) (Gray's test: p=0.009).

Conclusions

- HCT with PTCY platform showed a 32% of cumulative incidence of PE-BSI at 28 days and, splitting out by etiology, the cumulative incidence of GNB and GPB PE-BSI at 28 days were 14% and 23%, respectively.
- With PTCY platform, **donor type did not affect PE-BSI occurrence**
- By multivariate analysis, in subjects with **ANC ≤500 for ≥7 days before HCT** and with **MDR GNB rectal carriage** the risk of PE-BSI was more than double
- Haploidentical setting did not retain a higher IRM at 30 days than MRD and MUD transplants
- Active surveillance allow us to contain early KPC-*K. pneumoniae* attributable mortality
- PE-BSI attributable mortality is low and pathogen-related, but PE-BSI is associated with a higher IRM at 30 days; probably, this observation reflects the fact that PE-BSI is a marker of major comorbidities or systemic complications which justify the poorer clinical course

References

1. Mikulska M, et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of Gram-negative rods and increasing antibiotic resistance. *Biol Blood Marrow Transplant.* 2009;15:47-53
2. Blennow O, et al. Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations.*Transpl Infect Dis.* 2014;16:106-114
3. Girmenia C, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy. *Bone Marrow Transplant.* 2015;50:282-288
4. Girmenia C, et al. Incidence, risk factors and outcome of pre-engraftment Gram-negative bacteremia after allogenic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey. *Clin Infect Dis.* 2017;65:1884-96
5. Mikulska M, et al. Pre-engraftment bloodstream infections after allogeneic hematopoietic cell transplantation: the impact of T-repleted transplant from haploidentical donors. *Biol Blood Marrow Transplant.* 2018;24:109-118
6. Ciurea SO, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood.* 2015;126:1033-1040
7. Cieri N, et al. Post-transplantation Cyclophosphamide and Sirolimus after Haploidentical Hematopoietic Stem Cell Transplantation Using a Treosulfan-based Myeloablative Conditioning and Peripheral Blood Stem Cells. *Biol Blood Marrow Transplant.* 2015;21:1506-1514
8. Greco R, et al. Post-transplantation cyclophosphamide and sirolimus for prevention of GVHD after HLA-matched PBSC transplantation. *Blood.* 2016;128:1528-31