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ARTICLE

Severe infections and infection-related mortality in a large series of haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide

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Abstract

Severe infections and their attributable mortality are major complications in recipients of allogeneic hematopoietic stem cell transplantation (alloSCT). We herein report 236 adult patients who received haploSCT with PTCy. The median follow-up for survivors was 37 months. The overall incidence of bloodstream infections by gram-positive and gram-negative bacteria at 37 months was 51% and 46%, respectively. The incidence of cytomegalovirus infection was 69%, while Epstein Barr virus infections occurred in 10% of patients and hemorrhagic cystitis in 35% of cases. Invasive fungal infections occurred in 11% at 17 months. The 3-year incidence of infection-related mortality was 19%. The median interval from transplant to IRM was 3 months (range 1–30), 53% of IRM occurred >100 days post-haploSCT. Risk factors for IRM included age >50 years, lymphoid malignancy, and developing grade III-IV acute GvHD. Bacterial infections were the most common causes of IRM (51%), mainly due to gram-negative bacilli BSI. In conclusion, severe infections are the most common causes of NRM after haploSCT with PTCy, with a reemergence of gram-negative bacilli as the most lethal pathogens. More studies focusing on the severe infections after haploSCT with PTCy and differences with other types of alloSCT in adults are clearly warranted.

Introduction

Over the last decade, several haploidentical hematopoietic stem cell transplantation (haploSCT) strategies have been developed to overcome HLA barriers [1–4], improving the high incidence of graft rejection and graft versus host disease associated with earlier haploSCT experiences. Currently, haploSCT has become a real alternative for patients lacking identical donor, mostly after the introduction of post-transplant cyclophosphamide [5–11].

Bloodstream infections (BSI) are the most common severe infections and are a major cause of mortality in patients undergoing allogeneic hematopoietic stem cell transplantation (alloSCT) [12], with an incidence ranging from 13 to 46% [13]. Many risk factors for BSI and severe infectious complications exist, such as prolonged severe neutropenia, myeloablative conditioning regimens, severe mucosal damage, use of broad-spectrum antibiotics; acute graft versus host disease, prolonged corticosteroids, and previous infectious history [13–16]. Moreover, delayed immune recovery, as seen with ex-vivo T cell-depleted alloSCT leads to high incidence

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of late infections in the haploSCT setting, as reported with the Perugia platforms [1, 17].

Post-transplant cyclophosphamide (PTCy) was a major milestone in the haploSCT setting. PTCy removes selectively alloreactive donor T cells that are proliferating in response to host alloantigen while preserving non-alloreactive donor T cells [18], with surprisingly fast quantitative immune reconstitution [4, 19]. Despite initial encouraging results with PTCy [20], infection-related mortality (IRM) is still the most common cause of mortality, and possibly higher than in alloSCT from HLA identical sibling donor (21% vs. 13%, $p = 0.002$) [11]. Likewise, IRM was higher in haploSCT without PTCy than a matched cohort of recipients of HLA identical sibling alloSCT (26 + 6% vs. 10 + 4%, $p = 0.04$) [21].

Currently, despite several advances that have improved the outcomes after alloSCT, infectious complications remain a significant problem and a major cause of transplant failure.

In the present study, we describe the incidence of infections and causative pathogens in different post-SCT periods (pre-engraftment [<31 days] (PE), early post-engraftment [31–100 days] and late post-engraftment [>100 days]), the IRM and causative pathogens, as well as the overall transplant outcomes, in a large retrospective series of haploSCT with PTCy as graft versus host disease (GvHD).

Patients and methods

Patients

Two-hundred thirty-six adult consecutive patients were transplanted between November 2013 and November 2018 in six centers of the Spanish transplant group (Grupo Español de Transplante Hematopoyético [GETH]). All patients received a haploSCT using PTCy as GvHD prophylaxis [16] followed by calcineurin inhibitors, with or without mycophenolate mofetil (MMF). Transplants were done according to the local institutional protocols, and all patients signed informed consent. As a general rule, exclusion criteria were a poor performance status (ECOG ≥ 3 or Karnofsky score <60%), HIV infection, impaired cardiac or pulmonary functions, active viral hepatitis, and renal failure (creatinine > x 1.5 ULN). The information was evaluated retrospectively for each patient.

Conditioning regimens, Gvhd prophylaxis, and stem cell source

The conditioning regimens were selected by each institution according to patients' characteristics and local protocols. Myeloablative conditioning (MAC) regimens were fludarabine (40 mg/m^2 IV) from day −6 to −3 and busulphan (3.2 mg/kg IV) from day −6 to −3 (FluBu4) [22]; or thiotepa (5 mg/kg IV) on days −7 and −6, fludarabine (50 mg/m^2 IV) on days −5, −4, and −3 and busulphan (1 mg/kg/6 h on days −5, −4, and −3 oral dose, or 3.2 mg/kg/day IV dose on the same days) (TBF) [23].

Reduced-intensity conditioning regimens (RIC) consisted of fludarabine (30 mg/m^2 IV) from day −6 to −2, cyclophosphamide (14.5 mg/kg IV) on days −6 and −5 and busulphan (3.2 mg/kg IV) on days −4 and −3 (FluCyBu2). If the TBF platform was used as RIC, busulphan was reduced from three to 2 days (days −5 and −4).

All patients received PTCy (50 mg/kg IV on days +3 and +4) as GvHD prophylaxis followed by cyclosporine combined with MMF or tacrolimus alone since day +5 [22, 23]. Intravenous MESNA was given at a dose of 10 mg/kg/6 h on days +3 and +4 (total daily dose of 40 mg/kg) as hemorrhagic cystitis (HC) prevention.

Each institution chose to use either peripheral blood (PB) or bone marrow (BM) as the stem cell (SC) source. The target dose of CD34 + cells/kg of recipient weight to be infused was 5×10^6/kg (range 4–6 × 10^6/kg) in recipients of PBSC transplantation (PBSCT), while the target dose total nucleated cells (TNC)/kg recipient weight in BM recipients was 3×10^8/kg.

The centers selected the haploidentical donor based on availability and their preference among the first-degree relatives. Donor-specific anti-HLA antibodies (DSA) were studied in all patients; a local protocol of desensitisation was in place in case of inevitable high DSA titers were found (details not shown).

Definitions and supportive care

The definitions used in the current study are also shown in detail in the Supplementary online material.

In general, any bacterial, viral, or invasive fungal infection (IFI) requiring intravenous treatment or hospitalization was considered a severe infectious episode. In the case of common bacterial skin contaminants (mostly coagulase-negative staphylococci), a bloodstream infection (BSI) was diagnosed only if ≥2 consecutive blood cultures were positive for the same species. Infection data were collected retrospectively until the patient's death or last follow-up, using standardized definitions of severe infections after SCT based on the most recent guidelines (https://www.ebmt.org/working-parties/infectious-diseases-working-party-idwp). Common respiratory virus infections and virus-related hemorrhagic cystitis were also included in the study. Cytomegalovirus (CMV) infection was defined as the presence of at least 2 consecutive (within a minimum interval of 48 h) positive results of a

polymerase chain reaction (PCR) test for CMV in peripheral blood (PB) with a viral load >1000 IU/mL, while CMV disease was defined as the demonstration of CMV in biopsy or autopsy specimens from clinically involved visceral sites by culture and/or histology or if CMV was detected in samples from clinically-defined sites of disease. Epstein-Bar virus (EBV) infection was defined as the presence of at least 2 consecutive (within a minimum interval of 7 days) positive results of a PCR test for EBV in peripheral blood (PB) with a viral load >1000 e.g.c./mL, with or without evidence of EBV-related post-transplant lymphoproliferative disease (EBV-PTLD). Human herpes virus 6 disease was defined as the presence of positive PCR test in cerebrospinal fluid in patients with neurological symptoms (encephalitis), and a positive intestinal biopsy (colitis).

All patients were nursed in HEPA-filtered rooms. Antimicrobial prophylaxis was given following institutional policies, but which can be summarized as follows. Bacterial prophylaxis consisted of ciprofloxacin or levofloxacin during neutropenia or until the start of broad-spectrum antibiotics. Antifungal prophylaxis was administered according to the protocols at each site, with either fluconazole and a pre-emptive strategy; or a mold-active antifungal agent (posaconazole, voriconazole or other systemic antifungal drugs) until engraftment or whenever the patient was given steroids for the treatment of GVHD. Prophylaxis against *Pneumocystis jirovecci* consisted of cotrimoxazole until day −2 and then was restarted after engraftment. Pentamidine was used if cotrimoxazole was contraindicated. For prevention of Cytomegalovirus (CMV)-related disease, all institutions followed a preemptive approach with polymerase chain reaction (PCR) monitoring; the treatment started with positive PCR consisted of ganciclovir or foscarnet if severe neutropenia or ganciclovir toxicities. Acyclovir was recommended for a minimum of 1-year post-HSCT or until immunosuppressive therapy was stopped. Galactomannan testing and CMV PCR analysis were performed twice weekly, and Epstein-Barr virus (EBV) PCR analysis was performed weekly until day +100, in case of EBV infection, rituximab was used. Intravenous immunoglobulin (IVIG) replacement was recommended whenever the total IgG blood level was < 400 mg/dL, especially if the patient had prior infection by encapsulated bacteria or were considered to be at high risk of humoral immunodeficiency-linked opportunistic infections. All centers started the practice of vaccination after 6th months unless patients had severe active GvHD or were receiving IVIG therapy

Statistical analyses

SPSS statistics (IBM SPSS Statistics 21) and R studio programs (R studio, Boston, MA) were used for statistical analyses. Overall survival (OS) was defined as the time from day 0 to date of death by any cause, and progression-free survival (PFS) was the time from day 0 to disease progression or death. The Kaplan Meier method was used for estimating the actuarial PFS and OS, and the log rang test was used to study the univariate impact of any given variable on OS and PFS. The cumulative incidence (CI) estimate with competing risk(s) analysis was used to calculate the incidence of acute and chronic GVHD, non-relapse mortality (NRM), relapse, and infection-related mortality (IRM). The competing risk for NRM was relapse, while for relapse it was NRM. Competing risks for acute and chronic GvHD were disease relapse and NRM up to 100 days after stem cell infusion for acute GvHD and until the last follow up for chronic GvHD. Competing risk for IRM was NRM not due to infection or relapse. Competing risk of infection during a period of infectious risk was NRM or relapse during the time period. Gray test was used to study the impact of any given variable on a CI. We used landmark studies to find the incidence of infections in different time points, and thus time-dependent variables which occurred before each landmark point were included as binary variables. If the patients were alive at every time point they were categorized in two groups (with or without infection). Patients who died before the time of any given landmark point were excluded from the next time point. The time points: <day 31 (pre-engraftment), between days 31–100 (early post engraftment) and > day 100 (late post-engraftment) were used for infections by GPB, GNB, and conventional respiratory virus infection. For CMV and EBV, hemorrhagic cystitis and fungal infections, the time points selected were <31 and ≥31 days. COX regression analysis was used for multivariate analysis with documentation of proportional hazards over time for each outcome and covariate analyzed. In addition, variables or events that occurred post-transplant but before a given landmark point were analyzed as possible risk factors for IRM, NRM and relapse in the framework of Cox models as time-dependent covariates (for instance, occurrence of aGVHD), switching from absent to present at the moment of occurrence of each covariate/event.

Results

Patient and donor characteristics

Patient and donor characteristics are shown in Table 1. The median follow up of survivors was 37 months (range 12–82). The median patient age was 50 years (range 17–71), and 61% were male. Seventy-six patients (32%) had acute myeloid leukemia (AML), which was the most common underlying disease, followed by lymphoma in 70

Table 1 Patient and donors' characteristics.

Number of cases	**236**
Patients' characteristics	***N* (%)**
Median age [range]	50 (17–71)
Age ≥50 years/≥60 years	115 (49%)/57 (24%)
Male and female sex	144 (61%)/92 (39%)
Female donor to male recipient	64 (27%)
Underlying disease	
AML	76 (32%)
MDS	39 (17%)
ALL	22 (9%)
Non-Hodgkin's lymphoma	39 (17%)
Hodgkin disease	31 (13%)
CLL	8 (3%)
CML or other MPS	12 (5%)
Multiple myeloma	5 (2%)
Biphenotypic acute leukemia	2 (1%)
Aplasia	1
Prolymphocytic leukemia	1
Response at transplant	
Complete remission (first and second)	130 (55%)
Third complete remission	16 (7%)
Partial remission	33 (14%)
Stable disease	17 (7%)
Progression or refractory disease	33 (14%)
Induction chemotherapy aplasia	5 (2%)
Primary graft failure	2 (1%)
Refined Disease Risk Index (rDRI)	
Low rDRI	29 (12%)
Intermediate rDRI	125 (54%)
High rDRI	72 (31%)
Very High rDRI	7 (3%)
Prior HSCT, num. (%)	77 (33%)
Previous aloSCT	27 (11%)
Conditioning regimen	
FluBu	23 (10%)
FluBuCy	87 (37%)
TBF	121 (51%)
Other (FluCyTBI, FluATG)	5 (2%)
Conditioning intensity	
Myeloablative	75 (32%)
Reduced intensity	161 (68%)
Stem cell source	
Peripheral blood stem cells	191 (81%)
Bone marrow	45 (19%)
GvHD prophylaxis following PTCy	
Cyclosporine with MMF	115 (49%)
Tacrolimus	121 (51%)
	5,4 (1.95–11.42)
CD34 + cells infused (×106/kg) (median, range)	
Median follow-up in survivors, months (range)	37 [1–82]
Donors' characteristics	
Male and female sex	132 (56%)/104 (44%)
Donor relationship with patient	
Mother/Father	13 (6%)/23 (10%)
Son/Daughter	61 (26%)/41 (17%)
Brother/Sister	55 (23%)/39 (16%)
Other donors	4 (2%)
Donor and recipient CMV IgG combination	
D+/ R + −	112 (48%)
D−/R+	69 (29%)
D+/ R−	29 (12%)
D−/R−	25 (11%)

AML acute myeloid *MDS* Myelodysplastic syndrome, *ALL* acute lymphoblastic leukemia, *CLL* chronic lymphocytic leukemia, *CML* chronic myeloid leukemia, *MPN* myeloproliferative neoplasm, *HSCT* hematopoietic stem cell transplantation, *AlloSCT* allogeneic stem cell transplantation, *FluBu* fludarabine-busulfan, *FluBuBy* fludarabine-busulfan-cyclophosphamide, *TBF* thiotepa-fludarabine-busulfan, *Flu-CyTBI* fludarabine-cyclophosphamide-total body irradiation, *FluATG* fludarabine-ATG, *GvHD* graft versus host disease, *PTCy* post-transplantation cyclophosphamide, *MMF* mycophenolate mofetil, *CMV* cytomegalovirus, *D* donor, *R* recipient.

patients (30%). Twenty-seven patients (11%) had failed a first alloSCT.

One hundred thirty-five patients (57%) were in early disease phase at transplant (first and second CR; and post-induction aplasia), although 79 patients (34%) had a high or very high refined Disease Risk Index (rDRI) [24]. MAC regimen was used in 32% of the transplants (75 patients).

One hundred thirty-two donors (56%) were male, and the most common donors used was a son (26%) or a daughter (17%). An IgG seropositive CMV donor for a seropositive patient was the most frequent combination in 112 donor-patient CMV serostatus (48%), only 23% of patients were CMV seronegative.

Hematological recovery; acute and chronic GVHD

One hundred ninety-one patients (81%) received PBSC. The median number of CD34 + in PBSCT was 5.4×10^6/kg (range 1.95–11.42), while the TNC infused in BM recipients was 3.5×10^6/kg (range 0.84–19.6). The CI of neutrophil and platelet recovery was 94% (95% CI, 91–97%) and 90% (95% CI, 86–94%), respectively. Six patients (2.5%) had primary graft failure. Nine patients died early (before day +21) without engraftment (with a severe infection as primary cause of death), including 5/27 (19%) previously allotransplanted patients.

In the 221 remaining patients, the median time to neutrophil (>0.5 × 10^9/L) and platelet (>20 × 10^9/L) recovery was 18 days (range 9–49) and 26 days (range 10–156), respectively.

The CI of grade II-IV and III-VI acute GvHD at day +100 was 31% (95% C.I., 25–37%) (79 patients) and 11% (95% C.I., 7–15%) (30 patients), respectively; 5 patients died as a consequence of steroid-refractory grade III-IV acute GvHD.

The CI of limited, moderate, and severe chronic GvHD at 37 months was 16% (95% C.I., 12–22%), 8% (95% C.I., 5–11%), and 7% (95% C.I., 4–10%), respectively. Four patients died due to severe chronic GvHD.

Transplant outcomes

The OS at 12 and 37 months was 64% (95% C.I., 61–67%) and 50% (95% C.I., 46–54%), respectively, and the PFS was 57% (95% C.I., 54–60%) and 47% (95% C.I., 44–50%), respectively. Several variables had an independent impact on these outcomes in multivariate analysis (MVA); first and second CR at transplant, patients ≤ 50 years and grade III-IV acute GvHD for OS; and first and second CR at transplant, rDRI and patient age ≤ 50 years for PFS [Table 2].

The CI incidence of relapse at 12 and 37 months was 17% (95% CI, 12–22%) and 21% (95% CI, 16–26%), respectively. Variables that impacted on relapse in MVA were the disease response at transplant (first and second CR vs. other responses) and low-intermediate rDRI [Table 2]. Forty patients (17%) died owing to relapse.

The CI of non-relapse mortality (NRM) was 26% (95% CI, 21–31%) and 31% (95% CI, 25–37%) at 12 and 37 months. Prior alloSCT, age ≥50 years and grade III–IV acute GVHD were risk factors in the MVA [Table 2]. The main cause of NRM was an IRM (58% of NRM, 43 patients) [Table 3].

Infection-related mortality and severe infectious complications

The CI of IRM at 12 months was 17% (95% C.I., 12–22%) and 19% (95% C.I., 14–24%) at 37 months, and the variables with an independent impact in the MVA analysis were age ≥ 50 years, lymphoid malignancy as underlying disease (vs. myeloid), and development of grade III-IV acute GvHD [Table 2].

Six hundred twenty-three severe infectious episodes were reported in the 236 patients, with 2.6 infections per patient (range 0–8). Only 17 patients (7%) did not develop any severe infections. In addition, 14% (32 patients) developed a clinically defined severe infection without microbiological documentation, and 10% required ICU admission due to a severe infection.

Fifty-six percent of patients developed at least one bacterial infection (19% of patients had gram-positive bacterial infections, 15% had gram-negative bacterial infections, and 22% had both types of bacterial infections). CMV infection (CMV-I) was found in 69% of patients, and 52% had at least one non-CMV viral infection. An invasive fungal infection (IFI) occurred in 41 patients (17%), including 10% of possible, probable, or proven invasive aspergillosis. Specific pathogens involved, their distribution post-transplant, and the median time to onset of the major types of infections per time period are shown in detail in Table 4.

There were 43 cases of IRM; the median interval from transplant to IRM was 3 months (range 10–927); eight (19%) died during the PE period, 12 patients (28%) developed a lethal infectious complication in the early post-engraftment period, and 23 patients (53%) died beyond +100 days. In 51% (22 patients), the cause of IRM was bacterial, 16% (7 patients) developed a lethal viral infection, 5% (2 patients) an IFI, and two patients had a mixed bacterial and fungal infection. In 23% of clinically documented IRM no microbiological documentation was reported. The documented primary causes of IRM and NRM are shown in Table 3.

All IS was discontinued in 161 of patients (68%) at a median time post-transplant of 199 days (range 1–37 months), and seven of these patients died as a consequence of infection (4.3% IRM). Six of these seven patients died after day +100.

In 75 patients (32%) discontinuation of IS therapy had not been possible at last follow-up. Thirty-three patients died before 100 days, and the main causes of death were infection (19 patients, 25% IRM), while of the 42 patients who received IS drug/s after day +100, 17 died due to infections (40% IRM) and 12 patients were still alive at last follow-up more than 1 year post-transplant.

Bacterial infections

The incidence of PE (< day +31), early post-engraftment (day +31 to +100) and late post-engraftment (> day +100) infections by gram-positive bacteria (GPB) was 20% (95% C.I., 15–25%), 11% (95% C.I., 7–15%) and 20% (95% C.I., 14–26%), respectively, with an overall incidence of 51%. The median time of infection was 10 days (range 0–28), 72 days (range 32–97), and 7 months (range 3–29), respectively.

One hundred twenty-two infection episodes by GPB were reported (shown in detail in Table 4) of which 46% (56 episodes) occurred in the PE period. *Staphylococcus* spp. and *Enterococcus spp*. were the most frequent GPB. Six of seven patients with *Streptococcus spp*. infection in the late post-engraftment period were caused by *Streptococcus pneumoniae*. Only eight GPB (6%) presented antibiotic resistance (Methicillin-resistant *Staphylococcus*

Table 2 Univariate (UVA) and multivariate (MVA) analysis (37 months).

	IRM		NRM		Relapse		OS		PFS	
	UVA Incidence % (95% CI)	MVA (HR. 95% C.I.)	UVA Incidence % (95% CI)	MVA (HR. 95% C.I.)	UVA Incidence % (95% CI)	MVA (HR. 95% C.I.)	UVA Probability % (95% CI)	MVA (HR. 95% C.I.)	UVA Probability % (95% CI)	MVA (HR. 95% C. I.)
Disease status at transplant										
Complete remission (1st and 2nd)[a]	20 (13–27)	NA	27 (19–34)	NA	11 (5–16)	0.26 (0.14–0.5)	61 (57–65)	0.41 (0.28–0.6)	59 (54–64)	0.44 (0.3–0.63)
Other status/responses	18 (10–25)		36 (26–46)		35 (25–45)		34 (29–39)		31 (26–36)	
p value	0.1	0.7	0.07	0.05	0.001	0.001	0.001	0.001	0.001	0.001
rDRI										
Low-intermediate*	20 (13–26)	NA	30 (23–38)	NA	16 (10–22)	0.44 (0.24–0.79)	54 (50–58)	NA	52 (48–56)	0.64 (0.44–0.9)
High-very high	17 (8–25)		30 (19–40)		32 (21–42)		40 (34–46)		39 (33–45)	
p value	0.7	0.6	0.66	0.38	0.001	0.006	0.008	0.07	0.003	0.02
Prior alloSCT										
No*	18 (11–23)	NA	28 (22–34)	0.55 (0.33–0.9)	19 (14–25)	NA	52 (48–56)	NA	49 (45–53)	NA
Yes	26 (9–42)		44 (26–63)		26 (9–42)		29 (21–38)		29 (20–38)	
p value	0.3	0.3	0.02	0.02	0.3	0.8	0.001	0.117	0.001	0.09
Recipient years at transplant										
<50*	13 (7–199	0.34 (0.17–0.64)	25 (17–33)	0.5 (0.3–0.83)	21 (14–29)	NA	54 (49–59)	0.62 (0.43–0.9)	52 (47–57)	0.65 (0.45–0.9)
≥50	26 (17–34)		37 (28–46)		20 (12–28)		44 (39–49)		42 (37–47)	
p value	0.02	0.002	0.06	0.008	0.7	0.35	0.13	0.02	0.2	0.023
Grade 3–4 acute GvHD										
No*	17 (11–22)	0.47 (0.23–0.9)	26 (20–33)	0.41 (0.24–0.72)	21 (15–26)	NA	53 (49–57)	0.48 (0.29–0.78)	50 (46–54)	NA
Yes	36 (18–53)		58 (41–76)		17 (3–31)		28 (20–36)		24 (16–32)	
p value	0.03	0.05	0.001	0.002	0.6	0.22	0.007	0.003	0.02	0.07
Underlying disease										
Myeloid*	15 (9–22)	0.49 (0.26–0.9)	28 (20–36)	NA	18 (11–25)	NA	51 (46–56)	NA	50 (45–55)	NA
Lymphoid	23 (15–31)		33 (24–42)		24 (16–33)		49 (44–54)		44 (39–49)	
p value	0.1	0.032	0.4	0.8	0.34	0.72	0.4	0.7	0.24	0.3

[a]Reference variables in the MVA. In addition to the variables included in the table, other variables analyzed in the UVA and subsequently included in the MVA were: patient and donor sex, stem cell source, type of conditioning regimen (myeloablative vs. reduced-intensity), TBF conditioning vs. other, type of GvHD prophylaxis (tacrolimus vs. cyclosporine-MMF).

Table 3 Causes of nonrelapse mortality.

	Pre-engraftment (<31 days)	Early post-engraftment (31–100 days)	Late post-engraftment (>100 days)
Causes of IRM N 43 (58%)	**8 (19)**	**12 (28)**	**23 (53)**
Gram positive bacterial (N 7)	**2**	**3**	**2**
Enterococcus faecium	2		
Enterococcus faecalis		1	1
Streptococcus mitis		1	
Stretococcus pneumoniae			1
Methicillin resistance Staphylococcus aureus		1	
Gram negative bacterial (N 13)	**2**	**2**	**9**
Escherichia coli			1
ESBL Escherichia coli	1		
Pseudomonas aeruginosa			1
Multidrug resistance Pseudomonas aeruginosa	1	1	1
Klebsiella pneumoniae			2
ESBL or KPC Klebsiella pneumoniae		1	1
Acinetobacter baumannii			1
Stenotrophomonas maltophila			1
Serratia marcescens			1
Viral infection (N 7)	**1**	**3**	**3**
CMV disease (pneumonitis)	1	2	1
Metapneumovirus		1	
Human herpes 6 virus			1
EBV-PTLD			1
Invasive fungal infection (N 2)	**1**		**1**
Probable IFI	1		1
Gram negative bacterial + fungal infection (N 2)		**1**	**1**
Gram negative and positive bacterial (N 2)			**2**
Without positive microbiological (N 10)	**2**	**3**	**5**
Other causes of NRM N 26 (35%)	**4 (15)**	**9 (35)**	**13 (50)**
Graft rejection	1	2	2
Sinusoidal obstruction syndrome	2	1	
Idiophatic encephalitis		2	1
Refractory acute GvHD		2	3
Chronic GvHD			4
Other NRM causes	1	2	3
Secondary neoplasms N 5 (7%)			**5**

Other NRM causes: non-infectious endocarditis (x1), adult respiratory distress syndrome (x1), refractory bleeding (x1), alveolar refractory bleeding (x2) and sudden death (x1).

NRM non relapse mortality, *IRM* infection-related mortality, *ESBL* extended-spectrum beta-lactamase, *CMV* cytomegalovirus, *PT-LPD* post-transplant lymphoproliferative disorder, *EBV* Epstein-Barr virus, *IFI* invasive fungal infection, *PTLD* post-transplant lymphoproliferative disease.

Table 4 Microbiological etiology in time of onset.

	Pre-engraftment (<31 days)	Early post-engraftment (31–100 days)	Late post-engraftment (>100 days)
Total infectious episodes $N = 623$ (100%)	**205 (33)**	**214 (34)**	**204 (33)**
Gram positive bacteria $N = 122$ (20%)	**56 (46)**	**25 (20)**	**41 (34)**
Median time of GPB infections days or months (range)	10 days (0–28)	72 days (32–97)	7 months (3–29)
Staphylococcus spp	31	13	22
Enterococcus spp	17	10	10
Streptococcus spp	5		7
Corynebacterium spp	2		
Bacillus spp	1		
Listeria monocytogenes		2	1
Nocardia spp			1
Gram $N =$ egative bacterial N = 107 (17%)	**23 (21)**	**34 (32)**	**50 (47)**
Median time of GNB infections days or months (range)	13 days (0–28)	51 days (35–97)	7 months (3–33)
Escherichia coli	10	8	17
Pseudomonas aeruginosa	7	10	14
Klebsiella pneumoniae	2	7	8
Stenotrophomonas maltophilia	3	1	3
Serratia marcescens	1	2	1
Enterobacter cloacae		5	1
Haemophilus influenzae			4
Veillonella spp		1	
Acinetobacter baumannii			1
Leptotricia trevisanii			1
***Clostridium difficile* $N = 17$ (3%)**	**10 (59)**	**5 (29)**	**2 (12)**
Median time of CD infection days or months (range)	5 days (2–20)	42 days (32–47)	–
Viral infections			
Cytomegalovirus $N = 155$ (25%)	**58 (38)**	**84 (54)**	**13 (8)**
Median time of CMV infections days or months (range)	21 days (0–30)	42 days (31–100)	5 months (3–31)
Reactivation	54	84	12
Disease	4	–	1
Epstein–Barr Virus $N = 23$ (4%)		**5 (22)**	**18 (72)**
Median time of EBV infections days or months (range)	–	85 days (69–98)	5 months (3–20)
Reactivation	–	5	16
EBV-PTLD			2
Hemorrhagic cystitis $N = 77$ (12%)	**32 (42)**	**37 (48)**	**8 (10)**
Median time of HC infection days or months (range)	14 days (0–30)	45 days (31–98)	4 months (3–7)
BK Poliomavirus-related	20	31	3
Adenovirus	1	3	1
Without viral infection	11	3	4

Table 4 (continued)

	Pre-engraftment (<31 days)	Early post-engraftment (31–100 days)	Late post-engraftment (>100 days)
Upper respiratory tract viral infections $N = 34$ (5%)	**2 (6)**	**10 (29)**	**22 (65)**
Median time of URT infections days or months (range)	–	70 days (63–84)	10 months (4–42)
Influenza virus		5	10
Respiratory syncytial virus		5	2
Parainfluenza virus	1		6
Rhinovirus	1		2
Adenovirus			2
Lower respiratory tract viral infections $N = 28$ (4%)	**5 (18)**	**3 (11)**	**20 (71)**
Median time of LRT infections days or months (range)	17 days (19–22)	–	7 months (3–37)
Respiratory syncytial virus	2		8
Influenza virus	1	1	6
Parainfluenza virus		1	1
Coronavirus	1		1
Rhinovirus	1		3
Metapneumovirus		1	1
Other viral infections $N = 19$ (3%)	**5 (26)**	**5 (26)**	**9 (48)**
Median time of other virus infections days or months (range)	15 days (5–21)	63 days (40–93)	5,5 months (3–12)
Human herpes type 6 virus	1	3	3
Adenovirus	3		1
Rotavirus			2
Herpes simplex virus		2	
Hepes zoster virus			2
Enterovirus			1
Norovirus	1		
Invasive fungal infections $N = 41$ (7%)	**14 (34)**	**13 (32)**	**14 (34)**
Median time of fungal infections days or months (range)	10 days (0–28)	72 day (31–99)	11 months (4–46)
Possible IA	2	2	2
Probable IA	5	1	2
Proven IA	1	3	4
Pneumocystis jirovecci pneumonia			2
Candida spp uncomplicated fungemia	6	7	3
Penicillinum spp			1

GPB gram positive bacteria, *GNB* gram negative bacteria, *CD* clostridium difficile, *CMV* cytomegalovirus, *EBV-PTLD* EBV-related Post-transplant lymphoproliferative disease, *HC* Hemorrhagic cystitis, *URT* upper respirtory tract, *LRT* lower respiratory tract, *IA* invasive aspergillosis.

aureus (MRSA) and MR S. *epidermidis, with 4 infections each*). All GPB infections were BSI except for 3 cases of listeriosis and one case of nocardiosis.

There were 7 cases of IRM caused by GPB infections (16% of IRM), two infections before +30 days due to *Enterococcus faecium*, three in the post-engraftment period caused by *Streptococcus mitis, Enterococcus faecalis*, and MRSA and two late infections (> +100 days) due to *Enterococcus faecalis* and *Streptococcus pneumoniae* (shown in detail in Table 3).

With respect to infections by gram-negative bacteria (GNB), the incidence of PE (< day +31), early post-engraftment (day +31 to +100) and late post-engraftment (> day +100) infections was 10% (95% C.I., 6–14%), 14% (95% C.I., 9–19%) and 22% (95% C.I., 16–28%), respectively, with an overall incidence of 46%. The median time of infection was 13 days (range 0–28), 51 days (range 35–97), and 7 months (range 3–33). Details are shown in Table 4. One hundred seven GNB infections occurred, all were BSI, and as apposed to GPB infections the highest rate of GNB infections occurred in the late post-engraftment period risk, with 50 episodes (47%) of GNB infections. The most common pathogens isolated were *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, which accounted for 83/107 (78%) of GNB infections among these three species, 16% were antibiotic-resistant (eight multidrug-resistant (MDR) *Pseudomonas aeruginosa*, three extended-spectrum beta-lactamase producing (ESBL) *Escherichia Coli* and seven ESBL or carbapenamase producing *Klebsiella pneumoniae*). Other innately MDR species included 7 infections by *Stenotrophomonas maltophila* and one case of *Acinetobacter baumanii*.

The causes of IRM by GNB are shown in detail in Table 3, which accounted for 30% of IRM (13 patients); two lethal infections in the PE period (MDR *Pseudomonas aeruginosa* and ESBL *Escherichia coli)*, two in the early post-engraftment period (MDR *Pseudomonas aeruginosa*, and ESBL *Klebsiella pneumonia)*, and 9 patients in the late post-engraftment period (one *Pseudomonas aeruginosa* and one MDR *Pseudomonas aeruginosa*; one ESBL *Klebsiella pneumoniae* and two *Klebsiella pneumoniae*, one *Escherichia coli*, one S*erratia marcescense*, *Stenotrophomona maltophilia* and *Acinetobacter baumannii)*.

Virus infections

CMV and EBV Infections

The incidence of CMV infection (CMV-I) in PE period (< day +31) and post-engraftment period (≥31 days) was 25% (95% CI, 20–30%) and 44% (95% CI, 38–50%), respectively. In three patients were showed the CMV infection after 12 months. Among CMV seropositive patients the incidence of CMV-I was 78% (95% C.I., 72–84%), whereas it was 24% (95% C.I., 12–36%) in seronegative recipients. Five patients developed CMV pneumonitis, in four cases before day +31 and one on day +155, and four died from this complication.

The incidence of EBV reactivation was 10% (95% CI, 6–14%), mainly in the late post-engraftment period (18/23 cases). Fifteen patients were treated with rituximab due to high EBV DNAemia (>1000 e.g.c./mL). EBV-related post-transplant lymphoproliferative disorder (EBV-PTLD) was diagnosed in two patients and was lethal in one of these cases.

Community/conventional respiratory virus (CRV) infections

Sixty-two episodes of CRV infections were reported, and the incidence of at least one episode of CRV infection was 4% (95% C.I., 1–7%) in the PE period, 5% (95% C.I., 2–8%) in the early post-engraftment and 15% (95% C.I., 10–20%) in the late post-engraftment period. Only one patient died as a consequence of metapneumovirus pneumonia.

Upper (URTI) and lower (LRTI) respiratory tract infections by a CRV accounted for 34 and 28 episodes (55% and 45%), respectively (details shown in Table 4). Both URTI and LRTI occurred mostly in the late post-engraftment period (65 and 71% of CRV infections, respectively). The most CRV in URTI were influenza viruses (14 episodes), respiratory sincytial virus (7 episodes) and parainfluenza viruses (7 episodes), whereas respiratory sincytial virus (10 episodes) and influenza viruses (6 episodes) were the most common in LRTI.

Other viral infections

A very frequent complication in haploSCT protocols with PTCy is hemorrhagic cystitis (HC), as confirmed in the current study. The incidence of HC until +30 days was 14% (95% C.I., 10–18%) and after day +31 it was 21% (95% C.I., 16–26%), for an overall incidence of 35%. BK-polyomavirus-related HC was diagnosed in 54 cases (70% of HC), while adenovirus-related HC was found in five cases (6% of HC). No viral pathogen was identified in 18/77 cases of HC (23%), 11 of which occurred early post-transplant.

Human Herpes virus type 6 infection was diagnosed in 7 patients, with two cases of encephalitis and 5 cases of colitis. Other less common cutaneous and intestinal viral infections are shown in Table 4.

Invasive fungal infections

The incidence of invasive fungal infections (IFI) was 4% (95% C.I., 3–5%) before +31 days and 7% (95% C.I., 4–10%) after day +31, for a 3-year incidence of 11%. The most common IFI was invasive aspergillosis (IA), with eight cases of proven IA, eight probable IA and six cases of possible IA. An IFI was the primary cause of death for two patients with proven IA and one probable IA. *Pneumocystis jirovecci* pneumonia was diagnosed in the late post engraftment period in only two patients, while uncomplicated candidemia occurred in 16 patients (7%) [details in Table 4].

Discussion

In the current study, we describe the incidence of severe infections and the IRM in a large series of adult recipients of a haploSCT with PTCy. As previously described in other

studies infectious complications are the main cause of NRM, as occurs with other types of alloSCT [25, 26]. The 3-year incidence of NRM was 31% and 19% for IRM in the present study.

In our series, the 3-year incidence of GPB and GNB infections was 51% and 46%, respectively (246 episodes), similar to the incidence reported by others which range from 35% to 62% [27–30], albeit somewhat different definitions were used in different studies. The rates of GPB infections were similar in the pre-engraftment and late post-engraftment period, while GNB infections were more common in the late post-engraftment period (> day +100). Risk factors for these late GNB infections have been reported, although we did not analyze their risk factors due to the large number of species involved and thus small numbers per pathogen [14]. Bacterial infections were the most common causes of IRM (51%, 22 patients), mainly GNB infections (30%, 13 patients). As expected, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* were the most common GNB species [14, 27, 29, 31].

Antibiotic resistance appeared to contribute to IRM. A MDR strain was involved in 6/13 (46%) deaths by GNB, while only 16/83 (19%) overall isolated were MDR, and three additional patients died due to *Acinetobacter baumannii, Serratia marcescens, and Stenotrophomonas maltophilia*. Knowledge of the epidemiology of MDR GNB in each hospital as well as prior infections by these pathogens in any given patient is crucial in establishing the best empirical antibiotic strategy [14, 32, 33]. On the other hand, a high incidence of GPB was found during the study; however, antibiotic resistance was rare among GPB (6%), and only one patient died due to MRSA infection.

Regarding CMV-I, a high incidence was found in our series (24% during PE period and 45% beyond ≥31 days), in contrast to a low rate of CMV disease (2%), as reported by others [27, 29, 34–36]. A higher incidence of CMV-I in haploSCT with PTCy compared with other donor types has been reported previously [27, 36–38]. Initial studies hypothesized that the high incidence of CMV-I correlated with delayed CD4 + T cell and dendritic cell recovery [39, 40]. Also, CMV-I has a strong impact on the integrity and heterogeneity of the T cell repertoire, leading to CD8 + effector memory T cell expansion and contraction of naïve cells [41]. However, a recent report found that CMV-specific-T-cell reconstitution in T-cell replete haploSCT with PTCy was comparable to other types of alloSCT without PTCy [42]. More studies are necessary to define the relationship between CMV-I and immunological reconstitution.

Interestingly, we found a low incidence of EBV-I (10%) and EBV-PTLD (2 patients), as recently reported by other groups [27, 43]. The immunological hypothesis for the low incidence of EBV-I and EBV-PTLD is unclear, but the lack of in vivo or ex vivo T-cell depletion is of course a major determinant for the low incidence [42].

In haploSCT with PTCy the incidence of HC has been reported to range from 19% to 60% [38, 44]. Recent publications showed a higher incidence of HC in haploSCT with PTCy than in alloSCT from matched related donors also with PTCy (55% vs. 25%) [44, 45], suggesting that the use of PTCy is not the main risk factor for the higher incidence of HC in haploSCT. As expected, BK Polyomavirus was the most common virus linked to HC (70% of cases) in our series. In the haploSCT setting donor T lymphocytes are HLA mismatched with urothelial viral antigen-presenting cells, compromising the immune effector T cell response [45]. Although there is no treatment nor prophylaxis for viral-related HC, the continuous intravenous infusion of MESNA has been recently reported to reduce the incidence of HC when compared with bolus administration (5.6% vs. 27.8%) [46], although this requires confirmation with further studies.

A low incidence of IFI was found (11% at 3 years), especially during the early aplastic post-transplant period (4%) and with a very low impact on IRM. Due to the low incidence, we were unable to analyze the risk factors for developing an IFI.

Among the patients on immunosuppressive drugs (IS) during the entire study follow-up, 40% of all IRM (17 patients) occurred in patients after +100 days and 44% of all IRM occurred before day +100 (19 patients). However, in the 161 patients who discontinued IS post-transplant the IRM was low (7 patients, 4.3% rate of and 16% of all the cases of IRM).

The present study shares the limitations inherent to retrospective studies, including potential selection bias; and the uncertainty of whether all infections were captured and included in the study. However, the study gives a useful picture of the overall epidemiology of different severe infections and their impact on IRM in the setting of adult haploSCT with PTCy in our country.

In conclusion, our national study shows that IRM is the main cause of NRM in the haploSCT setting with PT-Cy. A major cause of IRM were GNB infections, possibly higher in patients with MDR GNB infections. Studies focusing on the immunological reconstitution, especially in patients without severe GVHD, may help in understanding the high incidence of late infections linked to cellular immunity, such as CMV and viral-related HC.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interest.

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References

1. Aversa F, Terenzi A, Tabilio A, Falzetti F, Carotti A, Ballanti S, et al. Full haplotype-mismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. J Clin Oncol. 2005;23:3447–54.
2. Federmann B, Bornhauser M, Meisner C, Kordelas L, Beelen DW, Stuhler G, et al. Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced intensity conditioning: a phase II study. Haematologica. 2012;97:1523–31.
3. Huang XJ, Liu DH, Liu KY, Xu LP, Chen H, Han W, et al. Haploidentical hematopoietic stem cell transplantation without in vitro T-cell depletion for the treatment of hematological malignancies. Bone Marrow Transpl. 2006;38:291–7.
4. Luznik L, O'Donnell P, Symons H, Chen AR, Leffell MS, Zahurak M, et al. HLA haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transpl. 2008;14:641–50.
5. Raiola AM, Dominietto A, di Grazia C, Lamparelli T, Gualandi F, Ibatici A, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. Biol Blood Marrow Transpl. 2014;20:1573e1579.
6. Ruggeri A, Labopin M, Sanz G, Piemontese S, Arcese W, Bacigalupo A, et al. Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia. Leukemia 2015;29:1891–900.
7. Ciurea SO, Zhang M-J, Bacigalupo AA, Bashey A, Appelbaum FR, Aljitawi OS, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood 2015;126:1033–40.
8. Kwon M, Bautista G, Balsalobre P, Sanchez Ortega I, Montesino P, Bermudez A, et al. Haplo-cord transplantation compared to haploidentical transplantation with post-transplant cyclophosphamide in patients with AML. Bone Marrow Transpl. 2017;52:1138–43.
9. Bashey A, Solomon SR. T-cell replete haploidentical donor transplantation using post-transplant CY: an emerging standard-of-care option for patients who lack an HLA-identical sibling donor. Bone Marrow Transpl. 2014;49:999–1008.
10. Brissot E, Labopin M, Ehninger G, Stelljes M, Brecht A, Ganser A, et al. Haploidentical versus unrelated allogeneic stem cell transplantation for relapsed/refractory acute myeloid leukemia: a report on 1578 patients from the Acute Leukemia Working Party of the EBMT. Haematologica 2019;104:524–32.
11. Bashey A, Zhang A, Jackson K, Brown S, Ridgeway M, Solh M, et al. Comparison of outcomes of hematopoietic cell transplants from T-replete haploidentical donors using post-transplantation cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 allele-matched unrelated donors and HLA-identical sibling donors: a multivariable analysis including disease risk index. Biol Blood Marrow Transpl. 2016;22:125–33.
12. Atilla E, Atilla PA, Bozdağ SC, Demirer T. A review of infectious complications after haploidentical hematopoietic stem cell transplantations. Infection. 2017;45:403–11.
13. Yan CH, Wang Y, Mo XD, Sun YQ, Wang FR, Fu H, et al. Incidence, risk factors, microbiology and outcomes of pre-engraftment bloodstream infection after haploidentical hematopoietic stem cell transplantation and comparison with HLA-identical sibling transplantation. Clin Infect Dis. 2018;67:S162–S173.
14. Girmenia C, Bertaina A, Piciocchi A, Perruccio K, Algarotti A, Busca A, et al. Incidence, risk factors and outcome of pre-engraftment gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an Italian Prospective Multicenter Survey. Clin Infect Dis. 2017;65:1884–96.
15. Herbers A, Haan A, van der Velden W, Donnelly J, Blijlevens N. Mucositis not neutropenia determines bacteremia among hematopoietic stem cell transplant recipients. Transpl Infect Dis. 2014;16:279–85.
16. Modi A, Rybicki L, Majhail NS, Mossad SB. Severity of acute gastrointestinal graft-vs-host disease is associated with incidence of bloodstream infection after adult allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2020;22:e13217.
17. Aversa F, Tabilio A, Velardi A, Cunningham I, Terenzi A, Falzetti F, et al. Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. N. Engl J Med. 1998;339:1186–9.
18. Luznik L, O'Donnell PV, Fuchs EJ. Post-transplantation cyclophosphamide for tolerance induction in HLA-haploidentical bone marrow transplantation. Semin Oncol. 2012;39:683–93.
19. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA haploidentical blood or marrow transplantation. Nat Rev Clin Oncol. 2016;13:10–24.
20. Raiola AM, Dominietto A, Ghiso A, Di Grazia C, Lamparelli T, Gualandi F, et al. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. Biol Blood Marrow Transpl. 2013;19:117–22.
21. Arcese W, Cerretti R, Sarmati L, Cudillo L, De Angelis G, Mariotti B, et al. Matched-pair analysis of transplant from haploidentical, unmanipulated bone marrow donor versus HLA identical sibling for patients with hematologic malignancies. Biol Blood Marrow Transpl. 2020;S1083-8791:30089–6.
22. Gayoso J, Balsalobre P, Kwon M, Herrera P, Bermúdez A, Sampol A, et al. Busulfan based myeloablative conditioning regimens for haploidentical transplantation in high risk acute leukemias and myelodysplastic syndromes. Eur J Haematol. 2018;101:332–9.
23. Esquirol A, Pascual MJ, Ortiz M, Piñana JL, Ferra C, Garcia Cadenas I, et al. Single-agent GvHD prophylaxis with tacrolimus after post-transplant high-dose cyclophosphamide is a valid option for haploidentical transplantation in adults with hematological malignancies. Bone Marrow Transpl. 2017;52:1273–9.
24. Armand P, Kim HT, Logan BR, Wang Z, Alyea EP, Kalaycio ME, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood 2014;123:3664–71.
25. Ullmann AJ, Schmidt-Hieber M, Bertz H, Heinz WJ, Kiehl M, Krüger W, et al. Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. Ann Hematol. 2016;95:1435–55.
26. Forcina A, Lorentino F, Marasco V, Oltolini C, Marcatti M, Greco R, et al. Clinical Impact of Pretransplant Multidrug-Resistant Gram-Negative Colonization in Autologous and Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transpl. 2018;24:1476–82.
27. Crocchiolo R, Bramanti S, Vai A, Sarina B, Mineri R, Casari E, et al. Infections after T-replete haploidentical transplantation and high-dose cyclophosphamide as graft-versus-host disease prophylaxis. Transpl Infect Dis. 2015;17:242–9.
28. Fayard A, Daguenet E, Blaise D, Chevallier P, Labussière H, Berceanu A, et al. Evaluation of infectious complications after haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide following reduced-intensity and myeloablative conditioning: a study on behalf of the francophone

society of stem cell transplantation and cellular therapy (SFGM-TC). Bone Marrow Transpl. 2019;54:1586–94.
29. Slade M, Goldsmith S, Romee R, DiPersio JF, Dubberke ER, Westervelt P, et al. Epidemiology of infections following haploidentical peripheral blood hematopoietic cell transplantation. Transpl Infect Dis. 2017;19:e12629.
30. Oltolini C, Greco R, Galli L, Clerici D, Lorentino F, Xue E, et al. Infections after allogenic transplant with post-transplant cyclophosphamide: impact of donor HLA-matching. Biol Blood Marrow Transpl. 2020;26:1179–88.
31. Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yanez L, et al. Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. Clin Infect Dis. 2017;65(11):1819–28.
32. Scheich S, Lindner S, Koenig R, Reinheimer C, Wichelhaus TA, Hogardt M, et al. Clinical impact of colonization with multidrug-resistant organisms on outcome after allogeneic stem cell transplantation in patients with acute myeloid leukemia. Cancer 2018; 124:286–96.
33. Goldsmith SR, Slade M, DiPersio JF, Westervelt P, Lawrence SJ, Uy GL, et al. Cytomegalovirus viremia, disease, and impact on relapse in T-cell replete peripheral blood haploidentical hematopoietic cell transplantation with post-transplant cyclophosphamide. Haematologica 2016;101:e465–e468.
34. Lin CH, Su YJ, Hsu CY, Wang PN, Teng CJ. Haploidentical allogeneic hematopoietic stem cell transplantation increases the risk of cytomegalovirus infection in adult patients with acute leukemia. Transpl Infect Dis. 2019;20:e13096.
35. Huntley D, Giménez E, Pascual MJ, Hernández-Boluda JC, Gago B, Vázquez L, et al. Incidence, features, and outcomes of cytomegalovirus DNAemia in unmanipulated haploidentical allogeneic hematopoietic stem cell transplantation with post-transplantation cyclophosphamide. Transpl Infect Dis. 2020;22:e13206.
36. Stasi A, Milton DR, Poon LM, Hamdi A, Rondon G, Chen J, et al. Similar transplant outcomes for AML/MDS patients with haploidentical versus 10/10 HLA matched unrelated and related donors. Biol Blood Marrow Transpl. 2014;20:1975–81.
37. Tischer J, Engel N, Fritsch S, Prevalsek D, Hubmann M, Schulz C, et al. Virus infection in HLA-haploidentical hematopoietic stem cell transplantation: incidence in the context of immune recovery in two different transplantation settings. Ann Hematol. 2015;94:1677–88.
38. McCurdy SR, Luznik L. Immune reconstitution after T-cell replete HLA-haploidentical transplantation. Semin Hematol. 2019;56:221–6.
39. Chang YJ, Zhao XY, Huang XJ. Immune reconstitution after haploidentical hematopoietic stem cell transplantation. Biol Blood Marrow Transpl. 2014;20:440–9.
40. Suessmuth Y, Mukherjee R, Watkins B, Koura DT, Finstermeier K, Desmarais C, et al. CMV reactivation drives post-transplant T cell reconstitution and results in defects in the underlying TCRβ repertoire. Blood. 2015;125:3835–50.
41. Huntley D, Giménez E, Pascual MJ, Remigia MJ, Amat P, Vazquez L, et al. Reconstitution of cytomegalovirus-specific T-cell immunity following unmanipulated haploidentical allogeneic hematopoietic stem cell transplantation with posttransplant cyclophosphamide. Bone Marrow Transplant. 2020;55:1347–56.
42. Kanakry JA, Kasamon YL, Bolaños-Meade J, Borrello IM, Brodsky RA, Fuchs E, et al. Absence of posttransplantation lymphoproliferative disorder after allogeneic blood or marrow transplantation using posttransplantation cyclophosphamide as graft-versus-host disease prophylaxis. Biol Blood Marrow Transpl. 2013;19(10): 1514–7.
43. Lunde LE, Dasaraju S, Cao Q, Cohn CS, Reding M, Bejanyan N, et al. Hemorrhagic cystitis after allogeneic hematopoietic cell transplantation: risk factors, graft source and survival. Bone Marrow Transpl. 2015;50:1432–7.
44. Copelan OR, Sanikommu SR, Trivedi JS, Butler C, Ai J, Ragon BK, et al. Higher incidence of hemorrhagic cystitis following haploidentical related donor transplantation compared with matched related donor transplantation. Biol Blood Marrow Transpl. 2019;25:785–90.
45. Arango M, Cardona D. Hemorrhagic cystitis after haploidentical transplantation with post-transplant cyclophosphamide: protective effect of MESNA continuous infusion. Biol Blood Marrow Transpl. 2020;26(8):1492–6.