Clostridioides Difficile Prophylaxis After Allogeneic Hematopoietic Cell Transplantation

Abby Kosharek, PharmD, MPA
PGY1 Resident
Barnes-Jewish Hospital

Objectives:

- Describe risk factors and complications associated with *Clostridioides difficile* infection after allogeneic hematopoietic cell transplant
- Discuss literature surrounding prophylaxis for *Clostridioides difficile* in patients who receive an allogeneic hematopoietic cell transplant

***C. difficile* Definition[1-2]:**

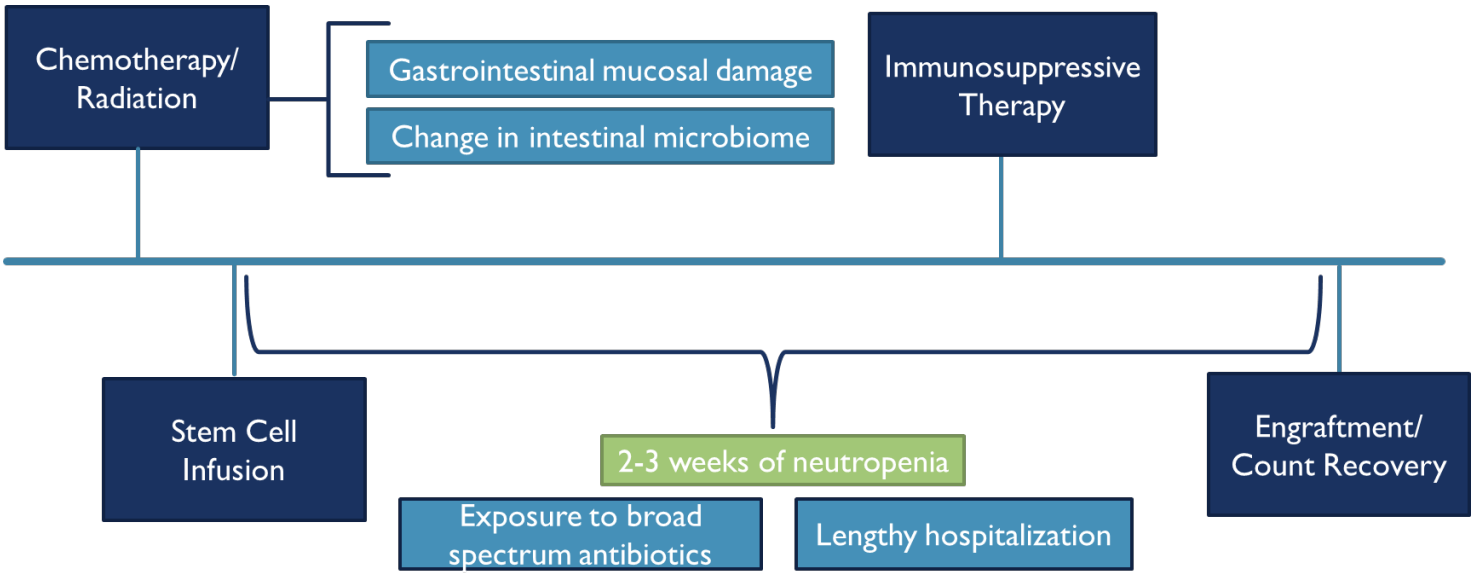
- Clinical Definition:
  - Positive *C. difficile* toxin stool test with $\geq$ 3 stools in 24 hours or diarrhea plus abdominal pain with other causes of diarrhea excluded
  - Pesudomembranes on endoscopy or histopathology

Vancomycin vs Fidaxomicin: Gut Microbiota[3]

Vancomycin	Fidaxomicin

▪ MOA: glycopeptide antibiotic that inhibits gram-positive bacteria cell wall synthesis (bacteriostatic)
▪ Gut microbiota:
  ▪ Leads to decreased intestinal microbiota diversity
  ▪ Promotes colonization by pathogens including VRE, *Klebsiella pneumoniae* and *E. coli*
	▪ MOA: macrolide antibiotic that inhibits RNA synthesis by RNA polymerase (bactericidal)
	  ▪ Higher in vitro activity against *C. difficile* with more prolonged post-antibiotic effects
	▪ Gut microbiota:
	  ▪ Less likely to promote colonization during CDI treatment
	  ▪ Narrow spectrum of action leads to selective target of C. *difficile* without disrupting normal microbiome

Risk Factors for *C. difficile* After alloHCT[4-7]:



Prevention Strategies[1, 8-9]:

Antimicrobial stewardship →

Febrile Neutropenia
-Start on broad spectrum antibacterial coverage
-Continue antibiotics until ANC ≥ 500 for 48 hours

Infection control measures →

-Contact precautions
-Personal protective equipment
-Hand hygiene with soap and water
-Proper cleaning and disinfection strategy

Prophylactic vancomycin or fidaxomicin →

Considerations For Any Prophylaxis:
- Treats common infection
- Effective medication
- Easy administration
- Limited toxicities
- Cost advantageous

Current Practice for *C. difficile*:
- Current standard of care is to not use routine prophylaxis at most centers
- No current guidelines on prophylaxis in alloHCT

Literature Review[10-12]:

Study	Purpose	Methods	Results
Ganetsky et al 2018	Evaluate effectiveness of oral vancomycin for *C. difficile* prophylaxis in alloHCT	Single-center retrospective cohort study between 2015-2016	**"Prophylaxis" group had 0 cases of CDI while on prophylaxis** VRE bloodstream infection rate was 1% in "prophylaxis" group and 4% in "no prophylaxis" group *C. difficile* infection at 90 days in "prophylaxis" group was 4%
Altemeier and Konrardy 2022	Evaluate effectiveness of oral vancomycin for *C. difficile* prophylaxis in alloHCT	Single-center retrospective cohort study between 2017-2019	**"Prophylaxis" group had CDI rate of 2% compared to 11% in "no prophylaxis" group** Incidence of VRE was 11% in "prophylaxis" group and 12% in "no prophylaxis" group CDI rate through day +100 was 8% in "prophylaxis" group and 15% in "no prophylaxis" group
Mullane et al 2018	Evaluate the efficacy and safety of fidaxomicin prophylaxis in auto- and allo-HCT	Randomized, double-blind, placebo-controlled, multi-center trial	**"Prophylaxis" group had CDI rate of 6% compared to 15% in "no prophylaxis" group in alloHCT** Mortality rate for "prophylaxis" group was 4% and 5% in "no prophylaxis" group Drug-related AE rate was 15% in "prophylaxis" group and 20% in "no prophylaxis" group

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Management of Patients Undergoing Hematopoietic Stem Cell Transplant after Solid Organ Transplant

Jesse Smith, PharmD
PGY-2 Solid Organ Transplant Resident, Barnes-Jewish Hospital
November 15th, 2022

Outline

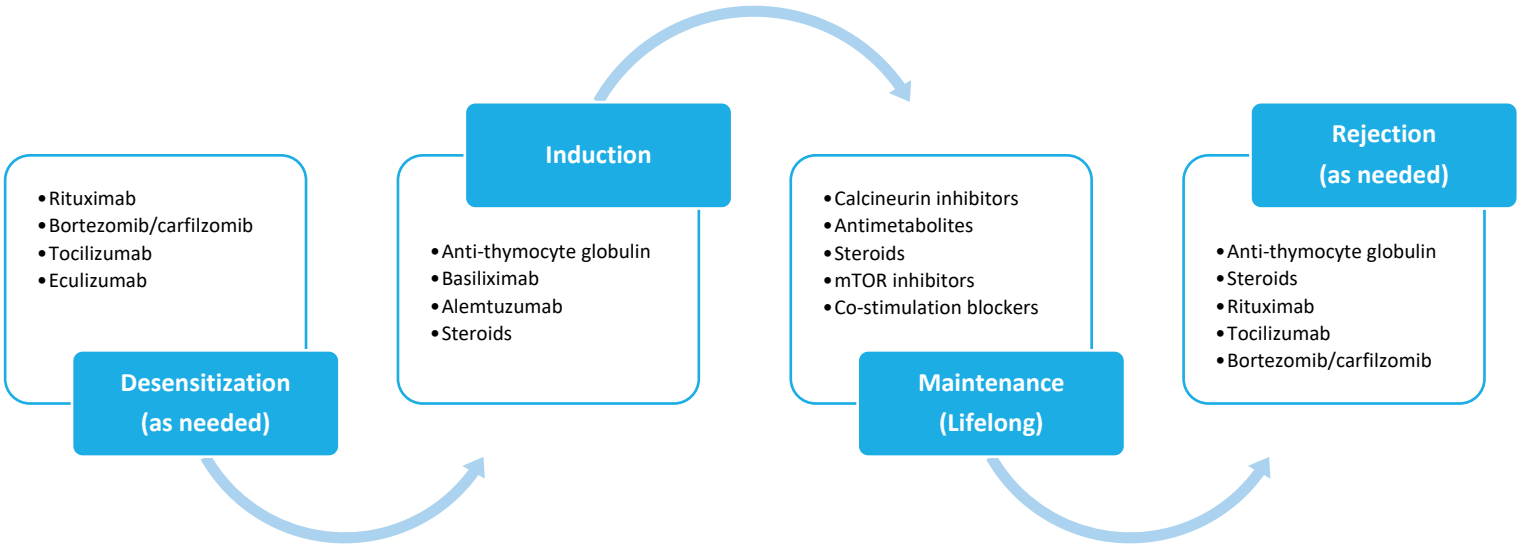
- Malignancy in solid organ transplant
- Hematopoietic stem cell transplant
- Immunosuppression strategies
- Literature review
- Final thoughts

Malignancy in Solid Organ Transplant

Risk Factors[1]

- Immunosuppression
- Viral infections
- Carcinogenic factors
- Donor transmission

Immunosuppression



Role of Immune System in Malignancy[2,3]

- Release of cancer cell antigens
- Cancer antigen presentation
- Priming and activation
- Trafficking and T cell to tumors
- Infiltration of T cells into tumors
- Recognition of cancer cells by T cells
- Killing of cancer cell

Hematopoietic Stem Cell Transplantation

Types[4,5]

- Autologous: stem cells are harvested from the recipient and cryopreserved to be later re-infused into the same individual after high dose chemotherapy with or without radiation
- Allogeneic: healthy unrelated or related donor with acceptable HLA compatibility

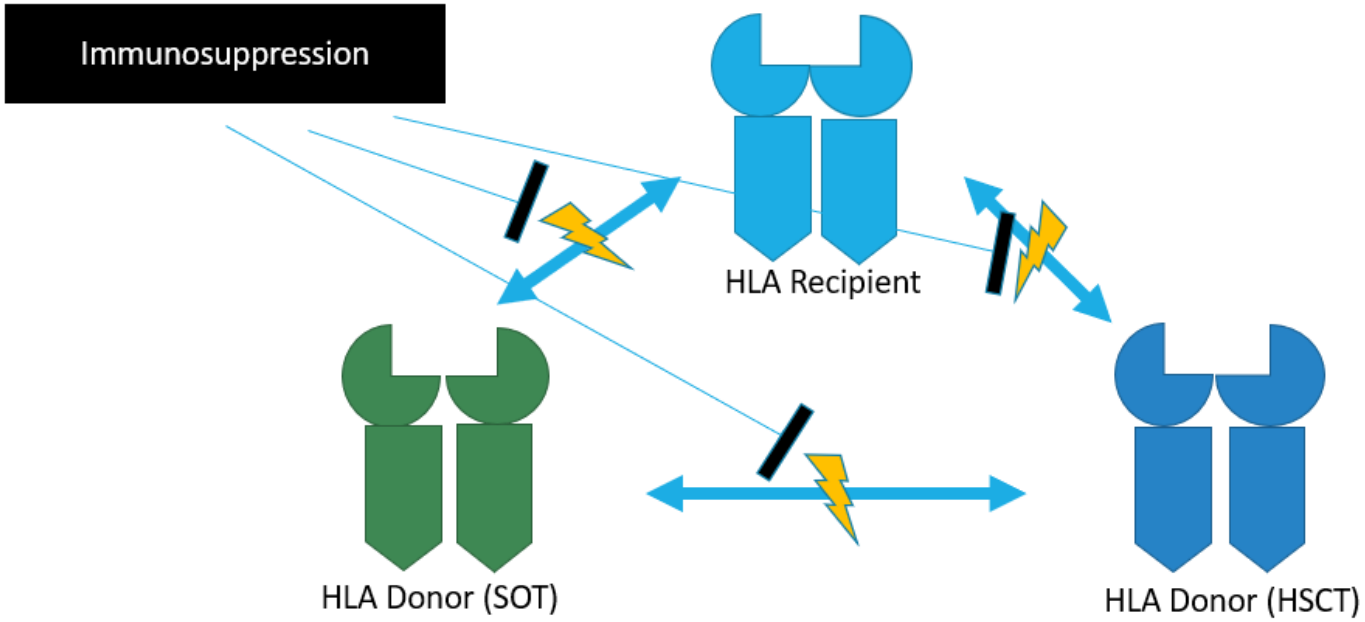
Process[4,5]

- Conditioning regimen
  - Ablate the recipient's native bone marrow and induce sufficient immunosuppression to allow for engraftment of infused stem cells
- Stem cell transplant
  - Ablate the recipient's native bone marrow and induce sufficient immunosuppression to allow for engraftment of infused stem cells
- GVHD prophylaxis
  - Immunosuppression

GVHD Risk Factors[6-8]

- Donor: haploidentical/mismatch unrelated
- Source: peripheral blood
- Conditioning: myeloablative

Human Leukocyte Antigen



Hematopoietic Stem Cell Transplant After Solid Organ Transplant: Immunosuppression

GVHD Immunosuppression Prophylaxis

- Calcineurin inhibitor
  - Tacrolimus
  - Cyclosporine
- Antimetabolite
  - Mycophenolate
  - Methotrexate
- Other therapies
  - mTOR inhibitor
  - Post-transplant cyclophosphamide
  - Antihemolytic globulin

Calcineurin Inhibitors

- Agent of choice
  - Tacrolimus
- Therapeutic drug monitoring
  - Compare GVHD goal vs SOT goal
  - Risk of GVHD, risk of rejection, organ transplanted, how far out from transplant?
- Duration
  - Lifelong

Antimetabolites

- Agent of choice
  - Mycophenolate
- Avoid agent specific toxicities
  - Azathioprine
    - Risk of relapse of malignancy
  - Methotrexate
    - Renal, lung, liver toxicity
    - Limited data in solid organ transplant
    - Limit duration and dose

Alternatives [9,10]

- Steroids
  - Not routinely used in the prevention of GVHD, mainstay of GVHD treatment
  - Role in solid organ transplant differs by organ
- Cyclophosphamide
  - Generally given 3-4 days post-haplo/matched sibling donor transplant
  - **Delay in immunosuppression**
  - Significant toxicities
    - Pulmonary injury
      - Rare: pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease
    - Cardiotoxicity
      - Oxidative stress to the myocardium and direct endothelial capillary damage
- mTOR inhibitors
  - Has also been linked to potential tumor suppressive properties
  - Limited data in suppression of hematologic disease

Hematopoietic Stem Cell Transplant After Solid Organ Transplant The Literature

Basak et al (2015)[11]

- Results
  - Overall survival at 60 months was 40% (95% CI, 19–60%)
  - Incidence of solid organ graft failure at 60 months was 33% (95% CI 16–51%)
  - Relapse rate of malignancy was 22%
- Conclusions
  - In select SOT with severe hematologic disorders alloSCT may contribute long-term survival without loss of organ function

Doney et al (2015)[12]

Allogeneic HSCT after SOT: Outcomes		
N, (%)	**Literature Review (n=27)**	**Fred Hutchinson (n=8)**
Survival after HSCT, yr, median, range	1.0 (0.1-8.0)	2.4 (0.4-23.1)
Death, total	8 (30)	4 (50)
Cause		
Rejection	1	0
Infection	4	0
Multiorgan failure	2	0
Persistent ALL/GVHD	1	0
Relapse of hematologic disease	0	4

El Jurdi et al (2021)[13]

N (%)	1-year Survival (95% CI) N=13	5-year Survival (95% CI) N=13
Survival		
Allogeneic	33% (8-62%)	33% (8-62%)

Cause of Death	
GVHD	3
Recurrent malignancy	3
Infection	2
Multiorgan failure	1

Literate Takeaways

- Although rare, hematopoietic stem cell transplant is a therapeutic strategy utilized by solid organ transplant recipients
- Very little to no recommendations for medication management

Immunosuppression Recommendations

- Patient-specific factors to consider
  - Organ transplanted
  - How far out from transplant?
  - Risk of GVHD/organ rejection

    - Infection
- Calcineurin inhibitor: tacrolimus
- Antimetabolites: mycophenolate
- Alternatives: cyclophosphamide, steroids, mTOR inhibitors

Final Thoughts

- Malignancy is a significant complication of solid organ transplant
- Hematopoietic stem cell transplant is a therapeutic strategy utilized by select solid organ transplant recipients with severe hematologic disease
- Immunosuppression in patients undergoing HSCT after SOT requires extensive knowledge of immunosuppression strategies in both fields while considering patient-specific factors

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Use of Post-Transplant Cyclophosphamide in Matched Unrelated Donor Allogeneic Transplant

Lauren Spreen, PharmD
PGY2 Oncology Resident
Barnes-Jewish Hospital
November 15th, 2022

Learning Objectives:

- Describe the incidence of and risk factors for GVHD in allogeneic stem cell transplant recipients
- Discuss the mechanism of PTCy in GVHD prevention
- Evaluate the literature of PTCy in combination with immunosuppressant agents for MUD allogeneic SCTs

Background:

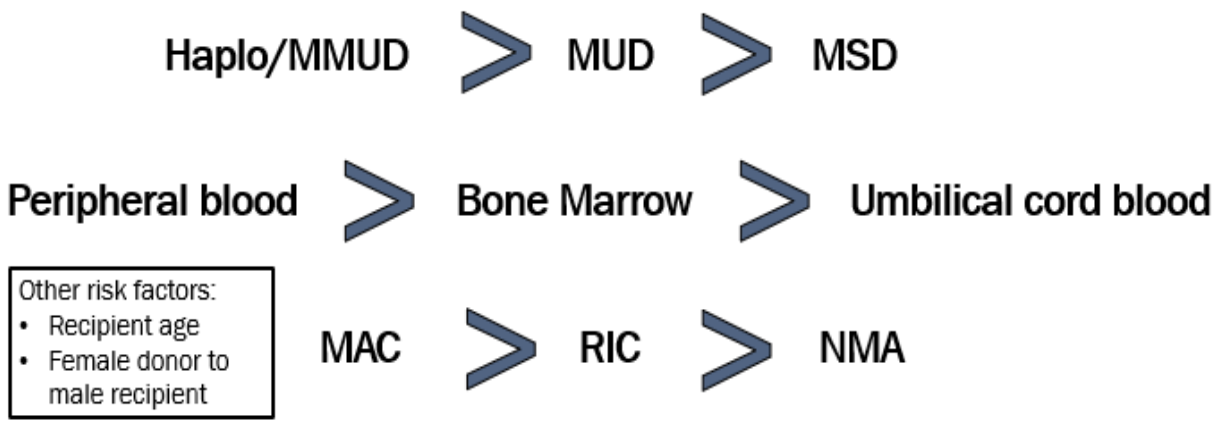
- Allogeneic stem cell transplant

Benefits of allogeneic SCT	Stem cell sources	Donor types	Conditioning Regimens
•Bone marrow rescue •Graft vs. leukemia effect •Curative/improves survival	•Peripheral blood (PB) •Bone marrow (BM) •Umbilical cord blood (UCB)	•Matched sibling donor (MSD) •Matched unrelated donor (MUD) •Mismatched unrelated donor (MMUD) •Haploidentical donor (haplo)	•Myeloablative conditioning (MAC) •Reduced-intensity conditioning (RIC) •Non-myeloablative conditioning (NMA)

- Graft Versus Host Disease
  - Classification

aGVHD	cGVHD
Usually develops within the first few months (<100 days) after transplantation or following a reduction of immunosuppression	Usually develops within the first year after SCT but can develop many years later
Characterized by maculopapular rash, GI complications, and hyperbilirubinemia	Characterized by fibrosis and other features resembling autoimmune disorders

  - Risk Factors



- Grading and Diagnosis

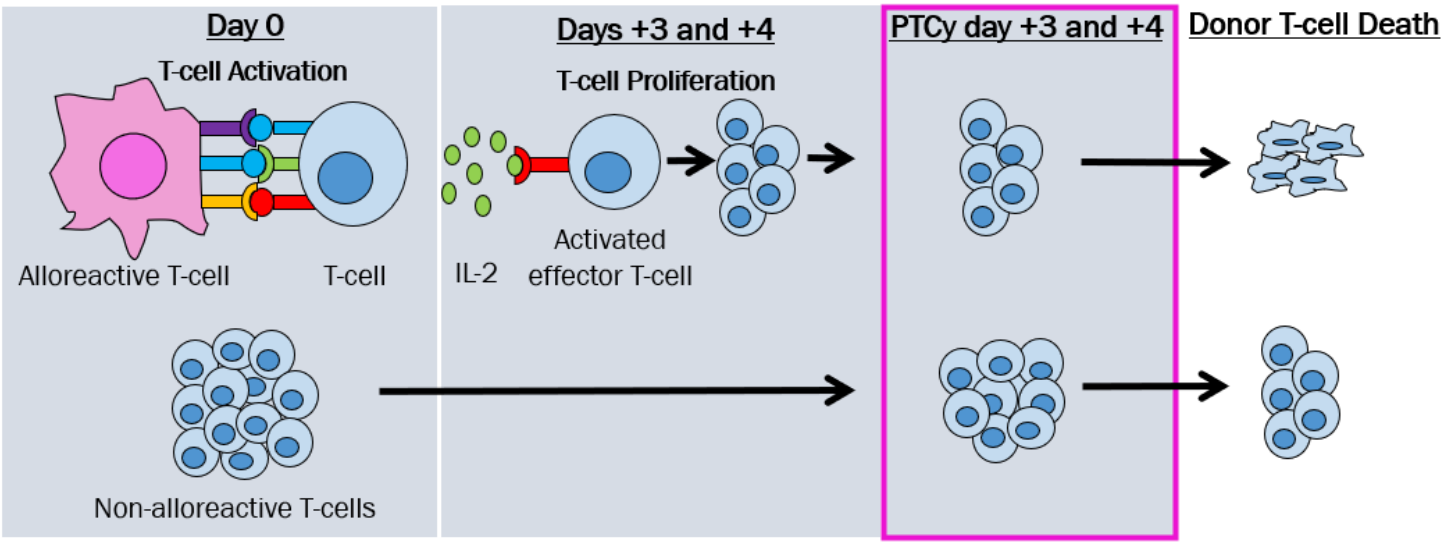
MAGIC Criteria: Acute GVHD Target Organ Staging & Overall Clinical Grade			
Stage	Extent of Organ Involvement		
	Skin	Liver	Lower GI (stool output/day)
0	No active GVHD rash	Bilirubin <2 mg/dL	<500 mL/day
1	Maculopapular rash <25% BSA	Bilirubin 2-3 mg/dL	500-999 mL/day
2	Maculopapular rash 25%-50% BSA	Bilirubin 3.1-6 mg/dL	1000-1500 mL/day
3	Maculopapular rash >50% BSA	Bilirubin 6.1-15 mg/dL	>1500 mL/day or >7 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus or grossly bloody stool

Grade (based on most severe target organ involvement)	
0	No stage 1–4 of any organ.
I	Stage 1–2 skin without liver, upper GI, or lower GI involvement.
II	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
III	Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI.
IV	Stage 4 skin, liver, or lower GI involvement, with stage 0–1 upper GI

Historic GVHD Prophylaxis in MUDs

	aGVHD Grade II-IV	aGVHD Grade III-IV	cGVHD	Bacterial/Viral/Fungal Infections
CNI-based regimens	65% **rates reported in additional studies range from 35-65%*	28% **rates reported in additional studies range from 17-28%*	33% **rates reported in additional studies range from 33-59%*	26%/15%/7%
ATG-based regimens	50% **rates reported in additional studies range from 27-57%*	28% **rates reported in additional studies range from 7-28%*	22% **rates reported in additional studies range from 3-26%*	13%/33%/5%

PTCy Mechanism of Action



1. After the stem cells are infused into the recipient, donor-alloreactive T cells become activated and rapidly proliferate and lead to the production of inflammatory cytokines.
2. Donor non-alloreactive T cells are also involved in this graft versus host response, but they are less proliferative.
3. This proliferation peaks around day +3 and +4.
4. PTCy is typically given on days +3 and +4 after transplantation when proliferation is at its peak.
5. This leads to donor T-cell death and prevention of GVHD.

PTCy Data in MUDs

	CNI-based Regimens	ATG-based Regimens	PTCy-based Regimens		
			Mehta	Gooptu	Salas
aGVHD Grade II-IV	65%	50%	48%	29-32%	18.2%
aGVHD Grade III-IV	28%	28%	6%	4%	5.7%
cGVHD	33%	22%	15%	25-29%	29.2%
Bacterial	26%	13%	37%	27% (MAC)	16.5%
Viral*	15%	33%	15%	NR	*5.7%
Fungal Infections (*CMV)	7%	5%	4%	1% (RIC)	4.5%
			2-year incidence rate	*day 180 incidence rate*	*day 180 incidence rate *CMV*

Mehta et al PTCy vs TAC/MTX/ATG Key Results

Efficacy Outcomes	MUD Cumulative Incidence (95% CI)		
	TAC/MTX/ATG (N=306)	PTCy (N=246)	*P*-value
aGVHD grade II-IV, day 180	42 (37-48)	52 (46-58)	0.03 ↑
aGVHD grade III-IV, day 180	9 (7-13)	8 (5-12)	0.4
Overall cGVHD, 3 years	19 (15-24)	18 (13-24)	0.5
Therapy-requiring cGVHD, 3 years	11 (8-15)	9 (6-14)	0.4
NRM, 3 years	23 (19-29)	13 (9-19)	0.002 ↓
Relapse, 3 years	28 (24-34)	29 (24-36)	0.9
PFS, 3 years	48 (42-53)	57 (51-64)	0.01 ↑
OS, 3 years	55 (49-61)	61 (54-67)	0.05 ↑
GRFS, 3 years	37 (32-43)	47 (40-54)	0.01 ↑

Safety Outcomes	MUD		
	TAC/MTX/ATG (N=306)	PTCy (N=246)	P-value
Neutrophil engraftment, median days	12	16	<0.001 ↑
Platelet engraftment, median days	14	23	<0.001
Bacterial infections at 6-months, %	44	53	0.01
Viral infections at 6-months, %	59	46	<0.001 ↓
CMV	35	24	0.002
EBV	11	2	<0.001
Fungal infections at 6-months, %	4	3	0.5
Grade ≥3 hemorrhagic cystitis, %	0	3	-----
Death, %			
GVHD	20	40	-----
Organ failure	28	17	-----
Bacterial infections	1	2	0.3
Viral infections	5	1	0.02 ↓

Recommendations

Use

- Adults or older adults who are undergoing a MUD SCT and receive
  - Peripheral blood stem cell source
  - Any conditioning regimen
- PTCy 50 mg/kg on days +3 and +4 in combination with CNI + MMF

Avoid

- Active infection at the time of transplant
- Recent fungal infection
- Currently on azole antifungals for an active fungal infection

Abbreviations:

95% CI	95% confidence interval
ADEs	Adverse events
aGVHD	Acute GVHD
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ATG	Anti-thymocyte globulin
BM	Bone marrow
BSA	Body surface area
cGVHD	Chronic GVHD
CI	Cumulative incidence
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CsA	Cyclosporine
EBV	Epstein-Barr virus
GI	Gastrointestinal
GRFS	GVHD-free/relapse free survival
GVHD	Graft versus host disease
HLA	Human leukocyte antigen
MAC	Myeloablative conditioning
MDS	Myelodysplastic syndrome
MMF	Mycophenolate mofetil
MMUD	Mismatched unrelated donor
MSD	Matched sibling donor
MTX	Methotrexate
MUD	Matched unrelated donor
NMA	Non-myeloablative
NR	Not reported
NRM	Non relapse mortality
OS	Overall survival
PB	Peripheral blood
PFS	Progression free survival
PTCy	Post-transplant cyclophosphamide
RFS	Relapse free survival
RIC	Reduced intensity conditioning
SCT	Stem cell transplantation
SOC	Standard of care
TAC	Tacrolimus
TBI	Total body irradiation
UCB	Umbilical cord blood

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