Infectious Complications After Hematopoietic Cell Transplantation

Lymphoma Tumor Board

March 10, 2017
Approximate immune cell counts (expressed as percentage of normal counts) peri- and post-myeloablative hematopoietic cell transplantation. Nadirs are higher and occur later after nonmyeloablative than myeloablative transplantation, as recipient cells persist after nonmyeloablative transplant for several weeks to months (in the presence of GVHD) or longer (in the absence of GVHD). The orange line represents the innate immune cells (e.g., neutrophils, monocytes, and natural killer [NK] cells), the recovery of which is influenced by the graft type (fastest with filgrastim-mobilized blood stem cells, intermediate with marrow, and slowest with umbilical cord blood). The green line represents the recovery of CD8+ T-cells and B-cells, the counts of which may transiently become supranormal. B-cell recovery is influenced by graft type (fastest after cord blood transplant) and is delayed by GVHD and/or its treatment. The blue line represents the recovery of relatively radiotherapy/chemotherapy-resistant cells such as plasma cells, tissue dendritic cells (e.g., Langerhans cells) and, perhaps, tissue macrophages/microglia. The nadir of these cells may be lower in patients with acute GVHD due to graft-versus-host-plasma cell/Langerhans cell effect. The red line represents CD4+ T-cells, the recovery of which is influenced primarily by T-cell content of the graft and patient age (faster in children than adults). From Storek J: Immunological reconstitution after hematopoietic cell transplantation – its relation to the contents of the graft. Expert Opinion on Biological Therapy (Informa) 8(5):583–597, 2008.
T-cell regenerative pathways after allogeneic HCT. Pretransplantation conditioning reduces the patient's existing naive (○) and memory (●) T cells.

Werner Krenger et al. Blood 2011;117:6768-6776
Normal thymic T-cell maturation and export

Thymus function in healthy young individuals

<table>
<thead>
<tr>
<th>Bone Marrow</th>
<th>Blood</th>
<th>THYMUS</th>
<th>Blood</th>
<th>Blood / Peripheral Lymphoid Organs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD3⁺CD4⁺CD8⁻ (TN)</td>
<td>CD4⁺CD8⁺ (DP)</td>
<td>Mature (SP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TCRB rearr. = DβJβ TRECs (●)</td>
<td>TCRAD rearr. = sj TREC (○)</td>
<td>sj/β ~100:1</td>
</tr>
<tr>
<td>HSC</td>
<td>Import</td>
<td>PROLIFERATION</td>
<td>DELETION</td>
<td>RTE Export (high RTE)</td>
</tr>
</tbody>
</table>

**Werner Krenger et al. Blood 2011;117:6768-6776**

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The effects of age and GVHD on T-cell maturation and export

Werner Krenger et al. Blood 2011;117:6768-6776
Risk of infectious complications after allogeneic HCT

- HCT is associated with high risk of mortality due to several factors: Regimen-related toxicity, infection, & graft vs. host disease (GVHD)
- Infection is reported as the primary cause of death in 8% of autologous HCT patients and 17-20% of allogeneic HCT recipients
- Risk assessments for posttransplant infection should be performed before transplant, taking into consideration:
  - Underlying disease, donor stem cell source, histoincompatibility, previous therapies, co-morbidities
- Myeloablative HCT recipients usually experience severe pancytopenia that can last days to weeks post HCT
- Time of neutrophil recovery depends on the type of donor stem cell graft
- Myeloablative regimens damage mucosal surfaces, which provide an environment in which pathogens can thrive
- Result is infectious complications in immediate posttransplant period that present with febrile neutropenia
Factors affecting the risk of infection after allogeneic HCT

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of transplant</td>
<td>Higher risk with allogeneic, lower risk with autologous or syngeneic, depending on graft manipulation and clinical setting, including previous therapies</td>
</tr>
<tr>
<td>Time from transplant</td>
<td>Lower risk with more time elapsed from transplant</td>
</tr>
<tr>
<td>Pre-transplant factors</td>
<td>Higher risk with extensive pre-transplant immunosuppressive therapy (e.g. fludarabine, clofaribine), prolonged pre-transplant neutropenia, or pre-transplant infection</td>
</tr>
<tr>
<td>GVHD</td>
<td>Higher risk with grade III–IV acute GVHD or extensive chronic GVHD</td>
</tr>
<tr>
<td>HLA match</td>
<td>Higher risk with HLA-mismatched donors, particularly with haploidentical donors</td>
</tr>
<tr>
<td>Disease (e.g., leukemia) status</td>
<td>Higher risk with more advanced disease at the time of transplant</td>
</tr>
<tr>
<td>Donor type</td>
<td>Higher risk with marrow unrelated donor than with a fully matching sibling donor</td>
</tr>
<tr>
<td>Graft type</td>
<td>Highest risk with cord blood, intermediate risk with bone marrow and lowest risk with colony stimulating factor-mobilized blood stem cells. Higher risk with T-cell–depleted grafts (depending upon method used)</td>
</tr>
<tr>
<td>Immunosuppression after transplant</td>
<td>Higher with immunosuppressive drugs, in particular with corticosteroids, anti-thymocyte globulin, alemtuzumab</td>
</tr>
<tr>
<td>Conditioning intensity</td>
<td>Lower risk in the first 1–3 months posttransplant with low dose chemo/radiotherapy</td>
</tr>
<tr>
<td>Neutrophil engraftment</td>
<td>Higher risk with delayed engraftment/non-engraftment</td>
</tr>
</tbody>
</table>
Common bacterial infections after allogeneic HCT

- Central Line-Associated Bloodstream Infections (CLABSI)
  - Catheter-associated infections are a leading cause of bloodstream infections
  - Prevention: antimicrobial/antiseptic ointments and antimicrobial lock prophylaxis
- *Streptococcus pneumoniae*
  - Can be life-threatening
  - Prevention: prophylactic antibiotics in patients with chronic GVHD
- Viridans streptococci
  - Prevention: Chemotherapy-induced oral mucositis can lead to viridans streptococcal bacteremia and sepsis. Dental consults are mandatory for HCT candidates to access their oral health.
  - Antibiotics given for a minimum of 21 days after transplant
- Enteric gram-negative organisms
  - Compromise of intestinal mucosal integrity due to conditioning regimen-associated damage and GVHD are important risk factors
  - Prevention: prophylactic fluoroquinolones when neutropenia develops
- *Haemophilus influenzae* type b
  - HCT recipients who are exposed to persons with Hib disease should receive prophylaxis with 4 days of rifampin or alternative antimicrobial. Droplet precautions.
Common viral infections after allogeneic HCT (1)

- **Cytomegalovirus (CMV)**
  - Shed from the oropharynx and the genitourinary track of both immunocompetent and immunosuppressed subjects.
  - Prevention: Prophylaxis to patients at risk post HCT. Ganciclovir, high-dose acyclovir, and valacyclovir have shown efficacy in preventing CMV reactivation
  - Use of CMV-seronegative donors and filtering blood products

- **Epstein-Barr Virus (EBV)**
  - EBV results from reactivation of endogenous infection or transmission of EBV from the graft
  - Monitor blood for EBV DNA load

- **Herpes simplex virus (HSV)**
  - Prevention: Acyclovir prophylaxis is mandatory for all HSV-seropositive allogeneic recipients to prevent HSV reactivation during the early posttransplant period.

- **Varicella-zoster virus (VZV)**
  - Prevention: Antiviral drugs such as long-term (~1 year) acyclovir prophylaxis to prevent reactivation of latent VZV
  - If reactivation, intravenous acyclovir until 2 days after all lesions have crusted over
Hepatitis viruses

Severe hepatitis B has been observed in HCT recipients in the following situations:

• "HBV-naïve HCT recipients exposed to HBV via an infected donor, infected blood products, or through sexual contact;

• HCT recipients with chronic hepatitis B experiencing prolonged immune suppression;

• HCT recipients with serological evidence of resolved HBV infection who have reverse seroconversion following prolonged immune suppression;

• HCT patients—generally in countries with endemic HBV—with latent occult hepatitis B (all serologic markers negative) that activates following prolonged immune suppression."

Pretransplant assessment for serologic evidence of infection with Hepatitis A, B, and C viruses is mandatory.
Human CMV virion structure and structural components

CMV viral load to start preemptive therapy (PET) used at the FHCRC in Seattle, WA, and the Karolinska Institute, Stockholm, Sweden.

<table>
<thead>
<tr>
<th>Immuno-suppression</th>
<th>CMV doubling time</th>
<th>Risk Groups</th>
<th>CMV Plasma DNA Level to Start PET at FHCRC*</th>
<th>CMV Whole Blood DNA Level to Start PET at Karolinska Institute**</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Short</td>
<td>Cord blood</td>
<td>Any level</td>
<td>1000 copies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allograft</td>
<td>&gt; 100 copies/mL</td>
<td>1000 copies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- High-dose steroids†</td>
<td></td>
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<td></td>
<td></td>
<td>- T cell depletion</td>
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<tr>
<td></td>
<td></td>
<td>- Anti-T cell antibodies</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>- CD34 selection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allograft</td>
<td>&gt; 500 copies/mL</td>
<td>1000 copies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Low dose steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No T cell depletion or anti T cell antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allograft</td>
<td>&gt; 1000 copies/mL</td>
<td>1000 copies if GVHD Other individual assessment based on ↑†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- after day 100</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>&gt; or 5-fold ↑†</td>
<td></td>
</tr>
</tbody>
</table>

* Assays performed weekly or twice weekly (highest risk); limit of detection 25 copies/mL
† 1 mg per kg of prednisone or higher
†† If initial level is less than threshold
** Assays performed weekly, limit of detection 50 copies/mL

Michael Boeckh, and Per Ljungman Blood
2009;113:5711-5719

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Mechanism of action of antiviral drugs for CMV

Pathogenesis of CMV drug resistance

- Low antiviral drug levels
  - Prolonged Drug Administration (before and/or after transplant)
  - Resistance

- Low immune status
  - Drug induced
  - T cell depletion (e.g. haploidental donor transplants)
  - Cord blood transplantation

Michael Boeckh, and Per Ljungman Blood
2009;113:5711-5719

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CMV drug resistance mutation maps

A

Codon 1 Nuclear Localization
337 345
Kinase domain
I
Putative function
ATP binding
P-Transfer
Substrate binding

MBVr
353 397 409.411
GCVr mutations
460 520 553
462 527 557
VIIb VII VIII IX

B

Functional domains
3'-5'-Exonuclease
Catalytic
Accessory protein binding

Codon range
379 492
421 588

Region
Exo IV/ExoII 8C/ExoIII II VI III I VII V

1 1243

Mutations in drug resistant isolates
D301N F412C D413E
N408D D413E
N408K D413A
N410K

Phenotype
GCVr CDVr
FOSr
GCVrCDVr

All listed mutations have been found in clinical isolates and validated by recombinant phenotyping

Michael Boeckh, and Per Ljungman Blood
2009;113:5711-5719
Map of the CMV DNA polymerase gene (UL54 or pol)


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MD Anderson Cancer Center proposed algorithm for management of refractory or resistant CMV infection with UL54 mutation(s)

- Refractory CMV or CMV drug resistance suspected
- CMV viremia (DNAemia or antigenemia) not improving or increasing after 2 weeks of adequate therapy in drug-naive patients
- OR
- New or worsening CMV end-organ disease with >6 weeks of therapy

- Was the patient receiving FOS?
  - YES
  - Add GCV (5 mg/kg twice daily intravenously, or corresponding dose adjusted dose for renal insufficiency)
  - AND
  - Consider continuing FOS
  - AND
  - Check for genotypic analysis for drug resistance
  - AND
  - Reduce immunosuppression if possible

- (+) UL54 mutation(s) (Figure 2)
  - GCV-FOS cross-resistance
    - Switch to CDV AND consider adding leflunomide as adjunct therapy, particularly for maintenance therapy
    - If no response or serious toxicities, consider one or a combination of investigational agents
  - GCV-CDV cross-resistance
    - Continue FOS AND consider adding leflunomide as adjunct therapy, particularly for maintenance therapy
    - If no response or serious toxicities, consider one or a combination of investigational agents
  - GCV-CDV-FOS cross-resistance
    - Continue FOS AND add high-dose GCV (x2 standard dose, i.e., 7.5 to 10 mg/kg twice daily intravenously or corresponding dose adjusted for renal insufficiency, consider G-CSF when using GCV) AND consider adding leflunomide as adjunct therapy, particularly for maintenance therapy
    - If no response or serious toxicities, consider one or a combination of investigational agents
  - FOS resistance
    - Stop FOS and continue GCV (5 mg/kg twice daily intravenously or corresponding dose adjusted for renal insufficiency) AND consider adding leflunomide as adjunct therapy, particularly for maintenance therapy
    - If no response or serious toxicities, consider one or a combination of investigational agents

Map of the cytomegalovirus UL97 gene

A

Phosphate transfer

ATP binding

Substrate binding

I  II  III

VIB  VII

VIII  IX

B

GCV\textsuperscript{R}

MBV\textsuperscript{R}

C592G
A594V/T/P/G/E
L595S/F/N
E596G
G598S
K599T
C603W/R/S
C607Y/F

In-frame codon deletions
591-594
591-607
595
595-603
600
601
601-603

V353A
L397R
L405P
T409M
H411Y/N/L

M460V/I/T
V466G

H520Q

Map units in codons

300  400  500  600  700

MD Anderson Cancer Center proposed algorithm for management of refractory or resistant CMV infection with UL97 mutation(s)

Therapeutic strategies for respiratory viral infections posttransplant

Upper respiratory tract infection

Specimen: Nasal wash/swab
Diagnostic test: Multiplex PCR

Pre-emptive therapy

Lower respiratory tract infection

Specimen: BAL fluid
Diagnostic test: Multiplex PCR + diagnostic panel*

Treatment of disease

Ongoing clinical trials for treatment of respiratory viral infections in patients with hematologic malignancy or HCT recipients

Risk-adapted strategy for antifungal prophylaxis

Marcio Nucci, and Elias Anaissie *Blood*
2014;124:3858-3869
Management of pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation

Radiographs of different types of nodular pulmonary lesions

References

- Recommendations of the Center for International Blood and Marrow Transplant Research (CIBMTR®), the National Marrow Donor Program (NMDP), the European Blood and Marrow Transplant Group (EBMT), the American Society of Blood and Marrow Transplantation (ASBMT), the Canadian Blood and Marrow Transplant Group (CBMTG), the Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the Association of Medical Microbiology and Infectious Diseases Canada (AMMI), and the Centers for Disease Control and Prevention (CDC), Tomblyn, M., Chiller, T., Einsele, H., Gress, R., Sepkowitz, K., ... Boeckh, M. A. (2009). Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplant Recipients: A Global Perspective. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*, 15(10), 1143–1238. [http://doi.org/10.1016/j.bbmt.2009.06.019](http://doi.org/10.1016/j.bbmt.2009.06.019)


