Hematopoietic Cell Transplantation
Managing Post-transplant

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Topics
1. Early and late complications
2. Treatments
3. Follow-up
4. Supportive services

Most Common Early-complications After Allogeneic Transplant
- Infection
- Acute graft-versus-host disease

Infection- early (first 100 days)
- Neutropenic sepsis- fever, often with positive blood cultures, will develop in nearly all patients within 7 days of becoming neutropenic. Sepsis usually caused by enteric bacteria or bacteria found on the skin. Antibiotics are continued until neutrophil count begins to rise (>500/ul).
- Prevention of fungal infections- for patients who are expected to have prolonged neutropenia, antifungal prophylaxis is used, including oral fluconazole (Diflucan 200 mg bid) or voriconazole (Vfend 200 mg bid). Liposomal amphotericin B or caspofungin/micafungin are other formulations used.
- Oral herpes simplex reactivation- nearly all patients who are seropositive for herpes simplex virus (HSV) will have a reactivation of the virus. To prevent this problem, most transplant programs use acyclovir during the neutropenic phase.

Infection- early (first 100 days)
- Cytomegalovirus viremia/infection- preemptive strategies have dramatically reduced morbidity and mortality.
- Pretransplant recipient CMV seropositivity most important risk factor for reactivation. (Transplant Infect Dis 2010;12:322)
- Most effective strategy to prevention reactivation of CMV infection is preemptive use of ganciclovir at the first sign of CMV after transplant. Duration somewhat controversial but usually for at least 2 weeks after CMV PCR assay becomes negative.
- Monitoring for CMV infection after therapy needed, esp pts with GVHD, cord blood recipients, T cell depleted transplant recipients
Acute graft-versus-host disease

- Clinical syndrome that results from infusion of immunocompetent lymphocytes in the stem cell graft that recognize minor HLA-related antigens in the host and initiate an immunologic reaction.
- Primary organs affected by acute GVHD are the skin, liver, and gastrointestinal tract.
- Occurs within 15-60 days after transplant and can vary in severity.

Prophylaxis: all patients who undergo non T cell depleted transplant require some form of GVHD prophylaxis

- Most common regimens involve a combination of methotrexate and cyclosporine or tacrolimus (Prograf).
- The combination of tacrolimus and sirolimus (Rapamune) appears to be an effective preventive approach without methotrexate.
- These medications, in the absence of GVHD, are tapered over 6 to 12 months after HCT.

Despite prophylaxis, many patients still develop some degree of GVHD and require increasing doses of prednisone (1 to 2 mg/kg/d).

There is no clear second line agent for steroid refractory acute GVHD.

- Table 1. Treatment of steroid-refractory acute GVHD

<table>
<thead>
<tr>
<th>Organ treated</th>
<th>GVHD manifestation</th>
<th>Secondary therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Intestinal</td>
<td></td>
<td>Tacrolimus</td>
</tr>
</tbody>
</table>

Most Common Late-complications After Allogeneic Transplant (>100days)

- Recurrent disease
- Secondary malignancy
- Chronic graft-versus-host disease
- Infection
- Cardiovascular and pulmonary complications

Significant stressors:
- Chronic pain
- Fatigue
- Insomnia
- Sexual dysfunction
- Memory loss
- Mood changes
- Vision and dental complications
- Financial stressors

Late Effects After Allogeneic Transplant

- Cataracts
- Keratoconjunctivitis sicca
- Thyroid cancer
- Hypothyroidism
- Bronchiolitis obliterans
- Chronic infections
- Liver dysfunction
- Hepatitis B, C
- Iron overload
- Sexual dysfunction
- Infertility
- Osteoporosis
- Avascular necrosis
- Membrane loss
- Depression/anxiety
- Post-traumatic stress disorder
- Dry mouth
- Oral cancer
- Renal failure
- Infections
- Recurrent malignancy
- Secondary malignancy
- GVHD
- Skin cancer

Relapse After Transplant Is Still The Primary Cause of Transplant Failure

CIBMTR Time Trends Study 2014

26,63 patients with acute leukemia, chronic myeloid leukemia and myelodysplastic syndrome.

<table>
<thead>
<tr>
<th>Outcome events</th>
<th>No. of patients at risk 1995-1999 (95% CI)</th>
<th>No. of patients at risk 2000-2003 (95% CI)</th>
<th>No. of patients at risk 2004-2007 (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>1 year 4598 20 (19-21)</td>
<td>5258 27 (26-28)</td>
<td>3972 27 (26-28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3 years 3742 26 (25-28)</td>
<td>2230 33 (32-34)</td>
<td>2400 34 (33-35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>5 years 3114 27 (26-28)</td>
<td>1714 34 (33-35)</td>
<td>977 37 (36-38)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Secondary Cancers

- AlloHCT survivors are at high risk for secondary leukemia, PTLD, new solid tumor at 2-4 times increased incidence compared to age-matched controls
- Particular high incidence exists for secondary oral cancers and thyroid cancers, especially in pts with chronic GVHD or prior irradiation

Late Effects Guidelines 2012 by CIBMTR

- Emphasis on regular age-appropriate cancer screening
- Earlier mammography recommended for women with h/o TBI, starting at age 25 years or 8 years after radiation
- Regular exam of the oral cavity and thyroid
- Increased risk of skin cancers – educate on importance of sunscreen protection and regular skin examination

Mujral, BMT 2012

cGVHD

- cGVHD incidence increasing despite advances in transplant practice
- Causes significant morbidity
- Skin involvement – sclerotic changes, fascitis or myositis complicated by joint contractures, visual issues, GYN complications, hepatitis, oral and intestinal involvement (diarrhea, anorexia), obstructive or restrictive lung disease
- Pathogenesis: highly complex immune pathology involving both donor B cells and T cells as well as other cells

Late Effects Guidelines 2012 by CIBMTR

- Occurs in:
  - 30% (young, with sibling donors) to
  - 70% (older, unrelated donors)
- Median time to development is 4-6 months after transplant
- 50% have 3 or more involved organs/tissues
- Risk factors: expansion of the donor population beyond HLA-identical siblings, older age patients, use of peripheral blood cells as graft source, donor and recipient gender disparity (female donor to male recipient), prior acute GVHD

Mujral, BMT 2012
cGVHD- what is new in diagnosis?

- cGVHD is primarily a clinical diagnosis. In 2005, new National Institutes of Health (NIH) Consensus Criteria were published (Filipovich BBMT 2005), designed to provide more detailed information about the individual organ involvement. A global score of severity (mild, moderate, severe) can be generated that is predictive of NRM and OS.
- 8 major organs involved: skin, mouth, eyes, genitalia, GI tract, liver, lung, muscles/fascia/joints.

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Table 1: Chronic GVHD-specific organ involvement

<table>
<thead>
<tr>
<th>Organ</th>
<th>Description</th>
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<tr>
<td>Skin</td>
<td>Sclerotic skin changes, nails, acral desquamation, mucosal changes in mouth, eyes, oral, anal, genital areas.</td>
</tr>
<tr>
<td>Mouth</td>
<td>Sclerotic skin changes, nails, acral desquamation, mucosal changes in mouth, eyes, oral, anal, genital areas.</td>
</tr>
<tr>
<td>Eyeball</td>
<td>Sclerotic skin changes, nails, acral desquamation, mucosal changes in mouth, eyes, oral, anal, genital areas.</td>
</tr>
<tr>
<td>Genitalia</td>
<td>Sclerotic skin changes, nails, acral desquamation, mucosal changes in mouth, eyes, oral, anal, genital areas.</td>
</tr>
<tr>
<td>GI tract</td>
<td>Sclerotic skin changes, nails, acral desquamation, mucosal changes in mouth, eyes, oral, anal, genital areas.</td>
</tr>
<tr>
<td>Liver</td>
<td>Sclerotic skin changes, nails, acral desquamation, mucosal changes in mouth, eyes, oral, anal, genital areas.</td>
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<tr>
<td>Lung</td>
<td>Sclerotic skin changes, nails, acral desquamation, mucosal changes in mouth, eyes, oral, anal, genital areas.</td>
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<tr>
<td>Muscles/Fascia/Joints</td>
<td>Sclerotic skin changes, nails, acral desquamation, mucosal changes in mouth, eyes, oral, anal, genital areas.</td>
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Sclerotic skin changes

Nails
cGVHD Treatment

- There is no FDA-approved treatment for aGVHD or cGVHD. The frontline treatment of choice for both in patients needing systemic therapy is steroids.
- For patients with cGVHD, the NIH Consensus Conference recommends systemic treatment with corticosteroids for those with moderate or severe disease.
- One mg/kg prednisone or equivalent is standard, but no randomized studies comparing this with an alternate dose exist.
- There are no consistent guidelines for tapering steroids for patients who have achieved a response.
- The median duration of therapy is 2–3 years.
- 15% still require therapy 7+ years after diagnosis.
- Attempts to improve on initial response rates have proven frustrating.
- Half of the patients require second-line treatment.

<table>
<thead>
<tr>
<th>Table 6. Agents used for secondary treatment of chronic GVHD</th>
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<tbody>
<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>EEP</td>
</tr>
<tr>
<td>Ruxolitinib</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Masotin (serum)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
</tr>
<tr>
<td>Interleukin-2</td>
</tr>
<tr>
<td>Interleukin-11</td>
</tr>
</tbody>
</table>

Other therapies mentioned in other reviews:
- Calcineurin inhibitors
- High-dose methotrexate
- Thalidomide
- Hydroxychloroquine
- Omalizumab
- Thiopurines
- Anti-TNP antibodies
- Infliximab
- Everolimus

* mTOR: mammalian target of rapamycin,
  **Simplified from Flowers et al, Woff et al, and Flowers and Deep for other reviews.
  ** 20%–60% overall response rates reported.

Blood 2015;125:606

Chronic GVHD Consortium

Clinical Sites:
- Fred Hutchinson
- University of Minnesota
- Dana-Farber Cancer Institute
- Vanderbilt University
- Medical College of Wisconsin
- H. Lee Moffitt Cancer Center
- Washington University
- National Cancer Institute
- University of North Carolina
- Weill Cornell Medical College
- Mayo Clinic
- Roswell Park Cancer Institute
- Cleveland Clinic
- Ohio State University

Consortium Clinical Trials

Bandage Lenses for eye chronic GVHD (N=20)

Randomized Phase II of imatinib vs rituximab for cutaneous sclerosis (N=74)

Longitudinal study of Immune Mediated Disorders (N=1,118)

Steroid-refractory chronic GVHD

Tocilizumab (N=20) – Genentech

Randomized Phase III of Restasis vs. Placebo for Prevention of ocular GVHD (N=264)

Phase II of FAM for BOS (N=49)

Steroid Meds providing drug

ORCID: CA1643348

[Image of clinical sites on a map]
Phase II Trial of Inhaled Fluticasone Propionate, Azithromycin, and Montelukast (FAM) for BOS

Change in individual and mean percentage FEV1 over time

FAM (Fluticasone propionate (440 mcg inhaled bid), Azithromycin (250 mg 3x/week), and Montelukast (10mg OD))

Primary endpoint was treatment success, defined as < 10% FEV1 decline at 3 months.

Eighty-three percent (n=30/36) had treatment success at 3 months.

Long Term Infectious Disease Concerns

- Pts with cGVHD have impaired opsonization, should be treated with abx prophylaxis against encapsulated organisms in addition to viral and PJP prophylaxis.
- All transplant pts should be given inactivated vaccines appropriate to their age, whereas live vaccines should be withheld in pts with cGVHD and impaired immunity.
- Live vaccines may be administered at 2 years post-HCT if it has been more than 1 year since receiving IS therapy and at least 5 mos since the last IVIG.
- The zoster vaccine (Zostavax) has higher viral titers and remains contraindicated.

Long Term Infectious Disease Concerns - Vaccinations

- Pneumococcal conjugate (PCV): may be given 3-6 mos
- Tetanus, Diphtheria, Acellular Pertussis: may be given 3-6 mos
- Inactivated influenza: yearly, may be given 4-6 mos
- Recombinant Hepatitis B: may give 6-12 mos
- Inactivated Polio: may give 6-12 mos
- MMR (live): all children and seronegative adults, may be given 2 years. Not recommended for patients with active GVHD and patients on immunosuppression.

Prevalence of metabolic syndrome 49%; a 2.2 fold increase over controls.

General Medical Care

- Pts with predisposing risk factors are at high risk for metabolic syndrome and CV disease- recommend heart-healthy lifestyle
General Medical Care

- **Pulmonary** complications - chronic infections to small airway destruction d/t cGVHD
- Initial post-transplant follow-up includes PFT, low threshold for chest imaging in pts with respiratory complaints
- Abstain from smoking
- **Liver**: cGVHD is a major complication of liver dysfunction. In pts surviving beyond 3 years, at least yearly LFTs
- **Kidney**: Routine screening for renal failure d/t calcineurin inhibitors
- **Skeletal** complications - high risk for osteoporosis - routine dxa scan, vit D-calcium. Routine use of bisphosphonates in pts with osteopenia
- **Eye**: Risk for cataracts, keratoconjunctivitis, sicca syndrome, retinopathy – annual eye exam
- **Oral**: Increased oral cancers and dental issues - annual oral and dental evaluations recommended
- **Endocrine**: Prevalence of hypothyroidism 20-40% - annual TFT

Additional Medical Conditions

**Chronic Pain**

**Emotional Distress**

**Financial Hardship**

Prevalence of HCT Survivors with Adverse Health Outcomes by cGVHD Status

Percentage of Subjects with Poor or Fair General Health According to Time Since HCT and cGVHD Status

Psychosocial and Psychological Issues

- Survivors likely to be burdened financially
- More likely to be unemployed than their peers
- Sexual dysfunction, infertility
- Shortage of transplant physicians to survivors
- Survivor clinics

Stanford Cancer Survivorship Program

**Clinics**

- Levels of service
  - Transition to survivorship
  - Manage long and late effects of cancer and its treatment

**Supportive Care**

- Survivorship Lecture Series
  - [cancer.stanford.edu/survivorship](cancer.stanford.edu/survivorship)
- Contact Kelly Bugos
  - kbugos@stanfordhealthcare.org
The care of HCT survivors requires a multidisciplinary approach that incorporates the expertise and resources of transplant centers, referring hematologists–oncologists, primary care physicians and other health care providers. Providers should integrate and involve their patients in this process, and ensure that they understand their risks and the surveillance required to prevent late complications.

BetheMatch.org

Stanford BMT Reunion

Last Saturday of Each July