Late Effects after a Transplant Using Your Own Cells (Autologous Transplant)

Celebrating a Second Chance at Life Survivorship Symposium

April 17-23, 2021

Late Effects of Autologous Hematopoietic Stem Cell Transplantation

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Objectives

• Review concept of autologous hematopoietic stem cell transplantation (AHSCT)
• Review common illnesses for which we transplant
• Review long term complications:
  – Immunologic/Hematologic issues
  – Late infectious complications/immunizations
  – Pulmonary (BCNU pulmonary toxicity)
  – Endocrine (thyroid, bone health, fertility)
  – Cardiac complications
  – Psychosocial issues
Indications for Hematopoietic Cell Transplant in the US, 2019

- **Allogeneic**
  - Myeloma / PCD
  - NHL
  - AML
  - MDS / MPN
  - ALL
  - HD
  - Non-malignant disease
  - Other malignancy
  - Aplastic Anemia
  - CML
  - Other Leukemia

- **Autologous**

*excludes aplastic anemia

Trends in Autologous HCT in the US by Recipient Age^

- **<18 Years**

- **18-39 Years**

- **40-64 Years**

- **65+ Years**

^Transplants for NHL, HD, MM

Visit www.bmtinfonet.org
Selected Disease Trends for Autologous HCT in the US

Trends in Survival after Autologous HCT for Follicular Lymphoma (FL), in the US, 2001-2018

Visit www.bmtinfonet.org
Tumor visible

The dose that can safely be administered is limited by effects on Normal Cells (sore mouth, diarrhea, low counts, infection and bleeding risk, liver, kidneys, heart)

Tumor invisible

Disease not Measurable = Remission
Getting to Remission

Remission (disease not visible by any standard testing)

These patients are not cured but their disease not detectable

This patient is cured but we don’t know that at the completion of therapy

Passage of Time Leads to Recurrence if not Cured after Initial Therapy

Remission

Cancer “recurs”

Resistant cells grow over time

“Cured”

Time
Goal of Stem Cell Transplantation

More malignant cells

Fewer malignant cells

No malignant cells

Remission/Near Remission

Administer further therapy beyond “capability” or intensity of conventional dose therapy

Conditioning Regimen (high-dose therapy)

Autologous Stem Cell Graft (collect pre therapy)

Time

Goal of Stem Cell Transplantation

More malignant cells

Fewer malignant cells

No malignant cells

Longer Remission

Prolong Remission

Prolong Survival

Cure

Time

Visit www.bmtinfonet.org
**Timeline for Stem Cell Transplantation**

- **6 Weeks**
  - Evaluation for transplant fitness
- **4-8 Days**
  - Chemotherapy
  - Restage/apheresis catheter
  - Growth Factor Collect cells
- **1-6 Days**
  - Days 6-10
  - High-Dose chemotherapy
- **10-14 Days**
  - Cell infusion (D0)
  - Side effects
  - Count recovery

**Components of Autologous Hematopoietic Stem Cell Transplant**

- **Preparative Regimen**
  - Chemotherapy
  - Possibly radiation
  - Variable intensities
- **Graft Source (autologous or syngeneic)**
  - Peripheral blood (stimulated by growth factor)
  - Bone marrow (rarely used or required today)
Rationale for AHSCT

Preparative Regimen + Rescue Product

Malignant Contamination

= Curative Potential + side effects

- Temporary Substantial bone marrow suppression
- Modest Degree of Immunosuppression
- Regimen-Related Side-effects Significant
- High-Dose Regimen is the Therapy; cells are support

Preventing Recurrence after Transplant

- Maintenance Treatments:
  - Rituximab (mantle cell lymphoma)
  - Lenalidomide (multiple myeloma)
  - Brentuximab (Hodgkin lymphoma)
- Consolidative Radiation
  - To one or two sites of disease that were “largest” pre transplant
Survey: Knowledge of Diagnosis and Post-Transplant Complications (3-25 years post transplant)

- 81% knew their diagnosis
- 99% knew the “components” of the transplant
- 90% were aware of most possible late effects
- 35% felt they had received follow-up surveillance/discussion of late effects
- Greater knowledge of late effects in the following patients:
  - Younger age at diagnosis
  - Mediastinal radiation
  - Those receiving follow-up care for late adverse effects

Survey: Knowledge of Post-Transplant Complications

(A) 100

Percent

Reduced fertility | Chronic fatigue | Secondary cancer | Cardiovascular disease | Hormonal changes | Other

[Bar chart data]

ACTA ONCOLOGICA 2019;58:1315
“Early” Post-Hospital Recovery Period

- Recover blood counts (days to weeks)
- Recover any other organ toxicity (e.g., kidneys)
- Remove apheresis catheter (days)
- Preventative antibiotics (acyclovir- months)
- Nutritional recovery (weeks to months)
- Muscle mass recovery (weeks to months)
- Begin re-vaccination series

Early to Middle Post-Hospital Recovery Period: Vaccination

<table>
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<tr>
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<th>9 mo</th>
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<td>Hep B</td>
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<td>x</td>
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<tr>
<td>Influenza</td>
<td>In season</td>
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<tr>
<td>Zoster</td>
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<tr>
<td>** MMR</td>
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<td>x</td>
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</table>
Risk of Zoster (Shingles) after AutoTransplant - Shingrix vaccine

![Graph showing cumulative incidence of shingles over time with Placebo and recombinant zoster vaccine compared.]

- 20%
- 10%

**JAMA 2019;322:123**

Early/Middle Post-Hospital Recovery Period - Lung Issues

“Idiopathic Pneumonia Syndrome”
- Older age at transplant
- Prior radiation or radiation as part of transplant preparative regimen
- Chemotherapy agents with risk:
  - BCNU (BEAM)
  - occasionally prior bleomycin
  - occasionally brentuximab
- Dry Cough, shortness of breath, reduced exercise tolerance
- Exam reveals “crepitations” or “crackles” (like squishing plastic wrap)
- Oxygen levels (saturation) may be normal or reduced
- Requires a high degree of suspicion and prompt evaluation
“Interstitial” Pattern of Injury

- ? Congestive heart failure
- Nasal washings for infectious causes
- Bronchoscopy for infectious causes
- Occasionally consider lung biopsy
- Treatment: Steroids (evidence is weak)
- Recovery can be complete

Case courtesy of Dr David Cuete, Radiopaedia.org, rID: 27858

Lung Function Studies

- 6% of asymptomatic subjects after autologous transplant
- 37% impaired gas transfer
- More likely if current smoker

ACTA ONCOLOGICA 2018; 57:773
https://medschool.co/tests/lung-function/flow-volume-loops
Immune Recovery after Transplant (30-365 days)

• WBC/neutrophils generally recover by 10-14 days (growth factor)
• Platelets slightly later; red cells generally last
• Lymphocytes (immune white cells) recover more slowly:
  • Cold sores (herpes simplex)
  • Shingles (herpes zoster)
  • Low immunoglobulin levels (bacterial infection) rarely a problem
  • Respiratory viruses may be more severe in this setting
• Infections relatively uncommon after recovery of cells except zoster (10-35% of patients)

Late Neutropenia (30-365 days)

• Low bacteria-fighting blood cell count
• 10 weeks or later post-transplant
• Can last weeks
• Rarely leads to infection
• Associated with prior rituximab (transplant and non-transplant setting)
• Occasionally antibiotics or white blood cell growth factors might be used
Late Bacterial Infections

- Uncommon
- Occasionally occur in setting of low immune proteins (immunoglobulins)
- Intravenous immune globulin (IVIG) may be used monthly to “fill” the body with the immune proteins it is not making
- Evidence for its benefit not strong in this setting

Risks for Osteoporosis

- Advancing Age/mobility
- Gender (Female)
- Ethnicity (Caucasian, Asian)
- Smoking
- Alcohol
- Early Menopause/early testicular hormonal failure (young at BMT)
- Prolonged steroids-highly uncommon in auto-transplant setting
- Myeloma is a special category
- Allogeneic transplantation is a different situation
- Investigations depend on disease and age at transplant
Bone Mineral Density after Autologous Transplant

- N=228 subjects Norway
- Bone Mineral Density post autologous transplant
- Age > 18
- Lunar Prodigy DEXA scan

**Compared to population database**

<table>
<thead>
<tr>
<th></th>
<th>Osteopenia</th>
<th>Osteoporosis</th>
<th>Population Osteoporosis</th>
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<tbody>
<tr>
<td>Male</td>
<td>35%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Female</td>
<td>41%</td>
<td>13%</td>
<td>11%</td>
</tr>
</tbody>
</table>

ACTA ONCOLOGICA, 2017;56;590

Breast Health

Chest radiation between 10-30 years of age may increase risk of breast cancer

- Highly dependent on technique, dose, size of field (different in 2020 vs 2000), genetic risk

After age 25:

- Clinical exam starting 8 years after RT
- Annual mammogram 8 yrs after RT but not until age 30
- Annual breast MRI 8 yrs after RT not until age 25
- Breast awareness/education- low evidence no harm
Female Sexual Health after Transplant

Female lymphoma subjects - average age 53 compared to control group
- More sexual problems compared to similar aged subjects without transplant
- More sexual discomfort
- Reduced frequency of sexual activity
- Had more sex-related fatigue
- Sexual activity associated with older age, being in a relationship
- Sex-related fatigue was related to being younger, having chronic fatigue, and having ongoing emotional distress

Bone Marrow Transplant 2019

Male Sexual Health after Transplant

Male lymphoma subjects - average age 55 compared to control group
- 39% reported sexual satisfaction
- 30% sexual drive only a few days per month
- 41% erections firm enough for sexual activity only a few times per month
- All BFSI (brief sexual function inventory) measures lower
- Presence of cardiovascular disease associated with worse erectile function
- Age > 55, chronic fatigue, physical inactivity associated with lower sexual functioning

Bone Marrow Transplant 2020
Fertility after Transplant

- Difficult to know “incidence” of infertility
  - survey
  - pre-existing conditions
  - unknown spousal fertility issues
- General Observations:
  - Can occur after regimens containing radiation
  - Fertility can return in both males and females, generally younger individuals
- Consider a safe waiting period (2 years)
  - Lack of menses does not mean infertility
  - always counsel and assume fertility!

Pregnancy Risks after Transplant

- Miscarriages similar to population expected (10%)
- Requirement for Cesarian section may be higher (30%)
- Requirement for assisted fertility techniques (20%)
- Risk of pregnancy-related complications appears similar
- Incidence of pre-term delivery appears similar
Working after Transplant

- Generally, recommendation is not to work first 3 months but depends on intensity of job
- Study: N= 274, mean age 52 years
  - 77% working pre-transplant
  - 69% working at time of survey
  - Employment pre transplant predicted for working post-transplant
  - Work hours did drop significantly post transplant
- We advocate short term disability if required and gradual return to full time hours with our input
- Our recommendations based on age, intensity of work, need to work

Secondary Cancers: Risk Factors

- Pre-existing risks (e.g., smoking, alcohol intake)
- Post-transplant maintenance therapy (lenalidomide-multiple myeloma)
- Males may be at more risk
- Early age may be greater risk
- Earlier era of transplant
Secondary Cancers: Types

- Second cancer risk varies by study and type of cancer
- Secondary MDS/AML likely the most common issue:
  - Extent of prior therapy
  - Age at transplant
  - Use of total body radiation (3% vs 10% at 10 years)
  - Prior alkylating agents
  - 5-10 fold increase
- Melanoma may have two-fold increase
- Non-Hodgkin Lymphomas up to three-fold increase

Secondary Cancers after AutoTransplant (n=7765)
Heart Health after AutoTransplant

- 10-year cumulative incidence:
  - Ischemic Heart Disease: 3.8%
  - Cardiomyopathy 6% (prior Adriamycin and dose may matter)
  - Stroke 3.5%

- Risks:
  - Pre-transplant smoking, BP, lipids, DM increased risk 1.5 fold
  - Persistence of abnormal BP and lipids at 1 year after transplant associated with increased risk

Summary of Long-Term Follow-Up

<table>
<thead>
<tr>
<th>Organ/System</th>
<th>What we Measure</th>
<th>What we Do</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid gland function</td>
<td>Thyroid levels (blood)</td>
<td>Treat-Thyroxine</td>
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<tr>
<td>Cataracts</td>
<td>Symptoms/periodic eye exam</td>
<td>Surgically remove- low risk</td>
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<tr>
<td>Bone Health</td>
<td>Fracture Risk/DEXA Testosterone</td>
<td>Calcium, Vitamin D/ Osteoporosis Rx</td>
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<tr>
<td>Breast Health</td>
<td>Mammography/MRI in some</td>
<td>Refer as appropriate</td>
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<tr>
<td>Oral</td>
<td>Dental Evaluations/x-rays</td>
<td>Dental Care</td>
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<th>What we Do</th>
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<tbody>
<tr>
<td>Heart Health (heart failure, coronary disease)</td>
<td>Blood Pressure, Lipid levels</td>
<td>Refer/treat as appropriate Stress tests/echo as required Stop smoking</td>
</tr>
<tr>
<td>Skin Health</td>
<td>Annual Skin Exam/sun health</td>
<td>Refer as appropriate</td>
</tr>
<tr>
<td>Secondary Cancers</td>
<td>Blood Counts, exams</td>
<td>Stop smoking, Investigate as needed</td>
</tr>
<tr>
<td>Fertility</td>
<td>Hormone levels</td>
<td>Pregnancy counseling/birth control</td>
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<tr>
<td></td>
<td>Semen Analysis</td>
<td></td>
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<tr>
<td>Immune System</td>
<td>Immune globulin levels if repeated infections</td>
<td>Infection prophylaxis Vaccines IVIG occasionally</td>
</tr>
</tbody>
</table>

Summary of Life after AHSCT

- Many feel they get back to near 100% of pre-transplant health
- Few are left with major life-altering medical issues
- Fertility can return in younger individuals
- Normal work life can resume
- Psychological health is important
- Age-appropriate health screening/vaccines
- Sun safety
- Appropriate follow-up for transplant-related medical issues
Celebrating a Second Chance at Life Survivorship Symposium 2021

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