Secondary Cancers

Celebrating a Second Chance at Life Survivorship Symposium

April 17-23, 2021

Secondary Cancers after Transplant: Overview

- What are secondary cancers?
- Who’s at risk after transplant?
- How often do secondary cancers occur?
- Monitoring and Prevention
- Treatment Options
Second Cancers after Transplant: Trying to Understand the Problem

- Study sizes and methods
  - Larger versus smaller
  - Length of follow-up
  - How good is the data?
- Concept of relative risk to population
  - Younger people have lower risk of cancer
- Potential to affect life expectancy
- Risk may be affected by many factors

General Factors Promoting Cancer Development

- Immune deficiency
- Aging
- Exposure to carcinogens
  - Viruses
  - Smoking
  - Alcohol
  - Sun
- Genetic predisposition
  - Family history
  - Telomere shortening
- Treatment with cancer promoting therapies
  - Drugs
  - Radiation
Factors That May Affect Cancer Risk after Transplant

- Underlying disease, prior therapies
- Donor versus own stem cells
- Drugs given to prevent GVHD
- Graft-versus-host disease
- Viral Infections – EBV, HPV
- Radiation use before or during transplant
- Higher-versus-lower dose transplant regimens
- Maintenance therapies after transplant

Secondary Cancers after Allogeneic Transplants (transplants using donor cells)
Patient Story

• 64 year-old gentleman from Colorado, indoor occupations
• DX with follicular NHL in 2004 at age 47, and myelodysplastic syndrome (MDS) in 2011 at age 54
• Had both cancers at time of transplant with matched sibling 2011
  • In remission of both diseases after transplant
  • Relapsed with myelodysplastic syndrome at 3 months
  • Treated with more chemo and tapering of immunosuppressants

Patient Developed GVHD

• Severe GVHD: skin, mouth, eyes
• GVHD gradually better but persistent, still on low-dose immunosuppressants
• Frequent skin cancers and scaly patches on skin
  – Squamous cell mostly, also a melanoma
  – Carcinoma on the tongue led to partial tongue resection
• Hard to tell difference between GVHD and pre-cancerous changes
Patient Now Disease-Free

• Check ups regularly
  – GVHD assessments
  – Dermatology visit every 3 months
  – Regular oral medicine visits
• No relapse of lymphoma or MDS

Secondary Cancers after Allogeneic Transplant (CIBMTR – 28,874 cases)

• 2nd cancers occurred at more than 2x expected rate of general population
• Highest excess risk in lip, salivary gland, tongue, bone, soft tissue and liver
• The relative risk for most solid tumors increased over time
• Increased risk with GVHD and radiation exposure at younger ages
Cumulative incidence of second solid malignancies after allogeneic HCT.

Demonstrates the need for long term health screening and monitoring

Most Common Solid Cancers after Transplant (EBMT (Europe) – 4,065 cases)

- Lung
- Breast
- Colorectal
- Prostate
- Melanoma

Ticelle at al, Jama Oncology 2019;5(2):229-235
Post-Transplant Lymphoproliferative Disorder

- Presents as a lymphoma usually in first year or two after transplant
- Associated with Epstein-Barr Virus (mononucleosis virus)
- Associated with more immunosuppressed transplants
  - T cell depleted
  - severe GVHD
  - cord blood
- May be treatable with rituximab, chemo, cell infusions

Secondary Cancers after Autologous Transplants (transplant using your own cells)
Risk Factors for Secondary Cancer after Autologous Transplant

- Age
- Type of cancer
- Pre-transplant therapies
- Stem cell collection
- Post-transplant therapies
  - Use of radiotherapy
    - for underlying disease
    - with transplant
Secondary Cancers in California Myeloma Patients
One Year Post-Transplant
3,202 transplant patients, 13,129 non-transplant patients

- Solid tumors
  - 3.6% at 5 years
  - 6.7% at 10 years
- Hematological tumors
  - 1.3% at 5 years
  - 2.7% at 10 years
- No overall increase in second cancers overall in transplant group vs. non-transplant group
- Slight increase in hematologic malignancy risk (1.5X)
- Very little effect on overall mortality
- Does not include effects of Revlimid maintenance


Revlimid Maintenance Therapy and Cancer

- Revlimid prolongs progression-free and overall survival
- Increases risk of new cancers
- “Lenalidomide increased the risk of a second primary cancer, but the survival benefits outweigh this risk.”
  Syed, Drugs 2017.
- Safer maintenance needed
Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) after Autologous Transplant

• Marrow damage from prior cancer therapy can lead to bone marrow cancer
• Risk increased after autologous transplant
  - *Infrequently seen after allogeneic transplants*
• Have high-risk genetic features and greater resistance to therapy
• Tend to occur in first 5 years after transplant

Risk of Myelodysplastic Syndromes (MDS) or Acute Myeloid Leukemia (AML) after Autologous Transplant

<table>
<thead>
<tr>
<th>Years post-transplant</th>
<th>Hodgkin Lymphoma (n = 916)</th>
<th>Non-Hodgkin Lymphoma (n = 3546)</th>
<th>Multiple Myeloma (n = 4566)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Risk 5-10 x background risk of normals

Treatment for Therapy–Related MDS and AML

Options depend on general health and prior therapies and include:

- Supportive care
- Drug therapy - generally not curative
  - Newer venetoclax-based therapies may extend survival
- Allogeneic transplant may cure or extend survival
  - Best outcomes when blast counts low

Other Maintenance Therapies and Cancer Risk

- Increasingly used after transplants to prevent or delay relapse
  - Rituxan after auto transplant for Mantle cell lymphoma
  - Brentuximab for Hodgkin disease
  - Vidaza after allo transplant for AML
  - Midostaurin after treatment for Flt-3 positive AML
- Weakens blood counts
- May suppress immunity
- May promote new cancers??
Pediatric Transplant Recipients

- Different diseases and treatment protocols
  - Autologous: Neuroblastoma, CNS tumors, lymphoma, other
  - Allogeneic: Immune deficiencies, enzyme deficiencies, acute leukemia, sickle cell, thalassemia
- Exposures to toxic therapies early in life while still growing
- Fertility/hormonal effects
- Genetic pre-disposition to cancer, e.g. Fanconi syndrome
- Solid tumors can occur > 20 years after transplant
- Different cancer screening protocols, beginning at an earlier age than recommended for general population

Late mortality after autologous transplant in childhood

![Graph showing cumulative incidence of late deaths from new cancers](image)

- Relapse-related mortality: 14.3% at 10y
- Non-relapse related mortality: 10.4% at 10y
- 21.4% of late deaths from new cancers

Holmqvist et al, Blood, 2018, Figure 2

Copyright © 2021 American Society of Hematology
## Outcomes after Secondary Cancers

Depends on:
- Type of cancer
- Age
- Stage at diagnosis
- Localized or not
- Surgery or radiotherapy cure?

- Effectiveness of drug therapy
- Comorbidities
  - Infections
  - GVHD
  - General health

## Outcomes

<table>
<thead>
<tr>
<th>Best (med survival &gt; 10 years)</th>
<th>Intermediate (med survival 6-10 years)</th>
<th>Worst (med survival &lt; 1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Colorectal</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Endometrial</td>
<td>Lung</td>
</tr>
<tr>
<td>Cervix</td>
<td>Sarcomas</td>
<td>Liver</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Ovarian</td>
<td>Esophagus</td>
</tr>
<tr>
<td>Prostate</td>
<td>Oropharyngeal</td>
<td>Brain</td>
</tr>
<tr>
<td></td>
<td>Bladder/Kidney</td>
<td>Stomach</td>
</tr>
</tbody>
</table>

A study from Japan showed:
- age of cancers developing was younger than of general populations
- poorer outcome of treatment than general population for allogeneic transplant recipients.

*Ticelle at al, Jama Oncology 2019;5(2):229-235
What Can You Do to Reduce the Risk of New Cancers after Transplant?

Reduce risk factors for cancer
  • Think of cancer developing as a multistep process
  • May be able to prevent or delay

Screening
  • Follow guidelines
  • Increased or early surveillance in some instances

Early Detection
  • Better chance of catching more treatable disease

Seven Steps to Prevent Cancer

1. Don’t use tobacco.
2. Protect your skin from the sun.
3. Eat a healthy diet.
4. Maintain a healthy weight and be physically active.
5. Practice safer sex and avoid risky behaviors.
7. Know your family medical history and get regular cancer screenings.

To learn more, please visit www.preventcancer.org
Cancer Screening for Transplant Survivors
Y. Inamoto et al, 2015

- www.ncbi.nlm.nih.gov/pmc/articles/PMC4989866
- A lot of detail on screening
- Reviews and compares
  - American Cancer Society
  - National Comprehensive Cancer Network
  - Consensus recommendations from CIMBTR and EBMT
- Ask your transplant team for guidance


Symptoms That Could Indicate Cancer

- New lumps or bumps
- Unusual fatigue, fevers, sweats
- Urination difficult, painful
- Cough, hoarseness, chest pain
- Bleeding anywhere, easy bruising
- Abdominal pain, bowel changes, loss appetite, trouble swallowing
- New blood clots
- Sores, new skin moles or lumps
- Headaches, vision changes, seizures, paralysis, numbness
Skin Cancers

- Probably commonest post-transplant cancer
- High level of vigilance post-transplant
- Prevent with sunscreen and sun avoidance
- Regular dermatology visits
- Early intervention is important
- Can be more aggressive than in people with normal immunity
- Can be hard to tell benign from more aggressive disease

Common forms of skin cancer

- Actinic keratoses (AK)
- Basal Cell Carcinoma (BCC)
- Squamous Cell Carcinoma (SCC)
- Malignant Melanoma

Images sourced from DermNet NZ
Oral Cancer

• Regular dental visits
• Consult oral medicine specialist if you have concerns – discuss with your physician

Breast Cancer

• Average Risk
  • age 20–40 years: Clinical breast exam every 1–3 years
  • age > 40 years: Annual clinical breast exam, Annual mammogram

• Prior chest radiation therapy or TBI:
  • Annual exam at age 25 years or 8 years after radiation therapy/TBI, whichever comes first, no later than age 40 years:
    – clinical breast exam
    – mammogram
    – breast MRI
Cervical Cancer

- Human Papilloma Virus (HPV) important
- Pelvic exams, cervix smears
- HPV Vaccine prevention in younger patients
- Annual Pap test and HPV DNA test

Liver Cancer – Risk Factors

- Cirrhosis
- Alcohol
- Hepatitis B – vaccinate/treat
- Hepatitis C - treat
- Iron overload (?)
  - Phlebotomy
  - Iron chelating drugs
Colorectal Cancer

- Treated by surgery, curable at early stage
- Tests
  - Colonoscopy
  - Sigmoidoscopy
  - Stool blood and DNA testing
- First colonoscopy recommended aged 45-50, screen up to 75 years
- Sigmoidoscopy every 5 years + FIT or high-sensitivity FOB
- More frequent if higher risk

Lung Cancer

- Smoking main risk factor
- Many patients will have had a chest CT done during treatment course
- Screening with low-dose CT of chest recommended for two high-risk groups:
  - $> 55$ years and $\geq 30$ pack-year smoking history
  - $\geq 50$ and have $\geq 20$ pack-year smoking history with one additional risk factor
Survivorship Planning

Written plan for recommended follow-up and self care

• Disease follow-up
• Healthcare maintenance and monitoring
• Vaccines
• Cancer screening
  • Delineate responsibility for cancer screening
  • Define plan based on risk factors
    • PCP important
    • Gynecologist
    • Oncologist/BMT physician
Summary

• Secondary cancers are an uncommon but important problem after transplants
• Autologous transplants - more marrow disorders
• Allogeneic transplants - more solid tumors
• Risk increases over time especially for solid tumors
• Long-term follow-up with screening and early detection may help avoid severe illness

Questions?

Celebrating a Second Chance at Life Survivorship Symposium 2021

bmtinfonet.org  help@bmtinfonet.org  847- 433-3313