CV Risk Alert in Hematologic Malignancies: Stem Cell Transplant and Cardiotoxic Exposures

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Hematologic Malignancies

**TABLE 1. Estimated New Cancer Cases and Deaths by Sex, United States, 2019***

<table>
<thead>
<tr>
<th></th>
<th>ESTIMATED NEW CASES</th>
<th></th>
<th></th>
<th>ESTIMATED DEATHS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTH SEXES</td>
<td>MALE</td>
<td>FEMALE</td>
<td>BOTH SEXES</td>
<td>MALE</td>
<td>FEMALE</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>82,310</td>
<td>45,660</td>
<td>36,650</td>
<td>20,970</td>
<td>12,100</td>
<td>8,870</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>8,110</td>
<td>4,570</td>
<td>3,540</td>
<td>1,000</td>
<td>590</td>
<td>410</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>74,200</td>
<td>41,090</td>
<td>33,110</td>
<td>19,970</td>
<td>11,510</td>
<td>8,460</td>
</tr>
<tr>
<td>Myeloma</td>
<td>32,110</td>
<td>18,130</td>
<td>13,980</td>
<td>12,960</td>
<td>6,990</td>
<td>5,970</td>
</tr>
<tr>
<td>Leukemia</td>
<td>61,780</td>
<td>35,920</td>
<td>25,860</td>
<td>22,840</td>
<td>13,150</td>
<td>9,690</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>5,930</td>
<td>3,280</td>
<td>2,650</td>
<td>1,500</td>
<td>850</td>
<td>650</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>20,720</td>
<td>12,880</td>
<td>7,840</td>
<td>3,930</td>
<td>2,220</td>
<td>1,710</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>21,450</td>
<td>11,650</td>
<td>9,800</td>
<td>10,920</td>
<td>6,290</td>
<td>4,630</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>8,990</td>
<td>5,250</td>
<td>3,740</td>
<td>1,140</td>
<td>660</td>
<td>480</td>
</tr>
<tr>
<td>Other leukemia‡</td>
<td>4,690</td>
<td>2,860</td>
<td>1,830</td>
<td>5,350</td>
<td>3,130</td>
<td>2,220</td>
</tr>
</tbody>
</table>

*Data from American Cancer Society.
Five-Year Survival Rates by Treatment Era

Radiation Therapy

Anthracyclines

Figure 2. Source: SEER (Surveillance, Epidemiology and End Results) Cancer Statistics Review, 1975-2014. National Cancer Institute; 2017.

*The difference in rates between 1975-1977 and 2007-2013 is statistically significant (p<.05).

"Survival rate among whites.

Cardiovascular complications

- Cardiac Dysfunction
- Atherosclerosis
- Arrhythmia
- Valvular disease
Impact of CVD on Cancer-Related Outcomes

Panel A.

<table>
<thead>
<tr>
<th>LVSD Status</th>
<th>5-year EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No LVSD</td>
<td>50.0%</td>
</tr>
<tr>
<td>LVSD, Infection-associated</td>
<td>36.5%</td>
</tr>
<tr>
<td>LVSD, Not infection-associated</td>
<td>32.8%</td>
</tr>
</tbody>
</table>

Panel B.

<table>
<thead>
<tr>
<th>LVSD Status</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No LVSD</td>
<td>66.0%</td>
</tr>
<tr>
<td>LVSD, Infection-associated</td>
<td>56.7%</td>
</tr>
<tr>
<td>LVSD, Not infection-associated</td>
<td>45.1%</td>
</tr>
</tbody>
</table>

**Leukemia**

- Cumulative incidence (%)
- Time (years)
- \( \text{P}<0.01 \)

**Lymphoma**

- Cumulative incidence (%)
- Time (years)
- \( \text{P}<0.01 \)

**Older (≥40 years) Cancers**

- \(5\text{y}: 22\% \text{ vs. } 16\%, \text{p}<0.01\)
- \(\text{IRR}^*: 1.7 \ (1.3-2.2)\)

**AYA (15-39 years old) Cancers**

- \(5\text{y}: 18\% \text{ vs. } 13\%, \text{p}<0.01\)
- \(\text{IRR}^*: 1.4 \ (1.1-1.8)\)

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**Multiple Myeloma**

- Cumulative incidence
- Time
- \(5\text{y}: 22\% \text{ vs. } 16\%, \text{p}<0.01\)
- \(\text{IRR}^*: 1.7 \ (1.3-2.2)\)

**Non-Hodgkin Lymphoma**

- Cumulative incidence
- Time
- \(5\text{y}: 18\% \text{ vs. } 13\%, \text{p}<0.01\)
- \(\text{IRR}^*: 1.4 \ (1.1-1.8)\)
CVD and All-Cause Mortality

Multiple Myeloma

NHL

Survival Function

Follow-up time (years)

P<0.01

No CVD

CVD

No CVD

CVD

CVD and Cause-Specific Mortality

Lymphoma survivors

A

- Excess DCS mortality
- Remaining excess mortality
- 95% CI

Diagnosed 19-35 yo

B

- Excess DCS mortality
- Remaining excess mortality
- 95% CI

Diagnosed 51-65 yo
Heart Failure

Coronary Heart Dz

Valvular Heart Dz

JNCI J Natl Cancer Inst, 2015, Vol. 107, No. 4
Hematopoietic Cell Transplantation (HCT)
CVD incidence over time in long-term HCT Survivors


Cardiovascular Death

Cardiomyopathy or Heart Failure

Ischemic Heart Disease

Stroke
Premature Vascular Disease in HCT Patients

- **Primary disease**
  - Familial risk factors
  - Pre-HCT exposures
  - Comorbidities

- **HCT**
  - Conditioning
  - GVHD

- **Clinical event**
  - De novo CV risk factors
  - Clinically apparent cardiovascular disease

**Vascular endothelial lesions**

**Enhancement of atherosclerosis**
Endothelial injury mediated by cytotoxic T lymphocytes and loss of microvessels in chronic graft versus host disease

Lancet 2002; 359: 2078–83

Figure 3: Circulating concentrations of von Willebrand factor (vWF)

Figure 5: Immune-mediated vascular injury in GVHD
Arterial disease by HCT type

Hypertension

Renal Disease

Dyslipidemia

Diabetes Mellitus
Role of Modifiable CV Risk Factors

Heart Failure–Free (probability)

No. at risk:
- 0 risk factors: 1,533 908 577 329 136
- 1 risk factor: 777 409 230 105 44
- ≥ 2 risk factors: 198 81 36 13 2

log-rank $P < .001$  

$\geq$ 2 CVRF  
1 CVRF  
No CVRF

Heart Failure  
Stroke  
Myocardial Infarction

$P < 0.01$

$\geq$ 2 CVRF
1 CVRF
No CVRF

$Blood$, 2012, 120: 4505-12
### Risk Prediction: CVD in HCT survivors

#### Variables (N=1,885)  
<table>
<thead>
<tr>
<th>Variable</th>
<th>Integer Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 30-&lt;50y</td>
<td>2</td>
</tr>
<tr>
<td>Age ≥50y</td>
<td>3</td>
</tr>
<tr>
<td>Anthracycline &gt;250 mg/m²</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
</tr>
<tr>
<td>Chest Radiation</td>
<td>1</td>
</tr>
</tbody>
</table>

#### AUC/C-Statistics: 0.72-0.80

![Cumulative Incidence](cumulative-incidence.png)
<table>
<thead>
<tr>
<th>Targeted cancer therapies</th>
<th>N ENGL J MED 375;15 NEJM.ORG OCTOBER 13, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 inhibitors</td>
<td>HER2 inhibitors</td>
</tr>
<tr>
<td>HER2 monoclonal antibody</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Newer HER2 inhibitors</td>
<td>Pertuzumab, trastuzumab emtansine, lapatinib</td>
</tr>
<tr>
<td>HER2</td>
<td>Decline in LVEF, congestive heart failure</td>
</tr>
<tr>
<td>VEGF signaling pathway inhibitors</td>
<td>VEGF signaling pathway</td>
</tr>
<tr>
<td>VEGFA monoclonal antibody</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>VEGF trap</td>
<td>Afibercept</td>
</tr>
<tr>
<td>VEGFR2 monoclonal antibody</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor with anti-VEGF activity</td>
<td>Sunitinib, sorafenib, pazopanib, axitinib, vandetanib, regorafenib, cabozantinib, lenvatinib</td>
</tr>
<tr>
<td>VEGF receptors (mainly VEGFR2) and other kinases; PDGFR</td>
<td>Hypertension, venous or arterial thromboembolic events, proteinuria, cardiomyopathy</td>
</tr>
<tr>
<td>Multitargeted tyrosine kinase inhibitors</td>
<td>Datasatinib</td>
</tr>
<tr>
<td>ABL, ABL mutants (except T315I), and other kinases; SRC, KIT, PDGFR, EGFR, BRAF, DDR1, DDR2, ephrin receptors</td>
<td>Pulmonary hypertension, vascular events, prolongation of QT interval corrected for heart rate</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>ABL, ABL mutants (except T315I), and other kinases; ABL2 (also called ARG), KIT, DDR1, NQO2</td>
</tr>
<tr>
<td>Coronary, cerebral, and peripheral vascular events, hyperglycemia, prolongation of QT interval corrected for heart rate</td>
<td></td>
</tr>
<tr>
<td>Ponatinib</td>
<td>ABL, ABL mutants (including T315I), and other kinases; FGFR, VEGFR, PDGFR, ephrin receptors, SRC, KIT, RET, TEK (also called TIE2), FLT3</td>
</tr>
<tr>
<td>Coronary, cerebral, and peripheral vascular events</td>
<td></td>
</tr>
<tr>
<td>Other multitargeted tyrosine kinase inhibitors</td>
<td>Crizotinib, ceritinib</td>
</tr>
<tr>
<td>Anaplastic lymphoma kinase inhibitors</td>
<td>Anaplastic lymphoma kinase</td>
</tr>
<tr>
<td>Bradycardia, prolongation of QT interval corrected for heart rate</td>
<td></td>
</tr>
<tr>
<td>PI3K–AKT–mTOR inhibitors†</td>
<td>Everolimus, temsirolimus</td>
</tr>
<tr>
<td>PI3K–AKT–mTOR signaling pathway</td>
<td>Cardiometabolic toxic effects, including hypercholesterolemia, hypertriglyceridemia, hyperglycemia</td>
</tr>
<tr>
<td>Bruton’s tyrosine kinase inhibitors</td>
<td>Ibrutinib</td>
</tr>
<tr>
<td>Bruton’s tyrosine kinase</td>
<td>Atrial fibrillation, other arrhythmias</td>
</tr>
<tr>
<td>MEK inhibitors</td>
<td>Trametinib, MEK1, MEK2</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Immunomodulatory drugs</td>
<td>Thalidomide, lenalidomide, pomalidomide</td>
</tr>
<tr>
<td>Lymphoid transcription factors IKZF1 and IKZF3</td>
<td>Venous or arterial thromboembolic events</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>Bortezomib, carfilzomib</td>
</tr>
<tr>
<td>Ubiquitin–proteasome system</td>
<td>Cardiomyopathy, hypertension, venous or arterial thromboembolic events, arrhythmia</td>
</tr>
<tr>
<td>Immune checkpoint inhibitors</td>
<td>Pembrolizumab, nivolumab</td>
</tr>
<tr>
<td>Programmed cell death 1</td>
<td>Myocarditis</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA4</td>
</tr>
<tr>
<td>Myocarditis</td>
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</tbody>
</table>
Advances in Imaging-Based Screening

PREVALENCE OF CARDIAC DYSFUNCTION AND REDUCED EXERCISE CAPACITY IN ADULT, 10-YEAR SURVIVORS OF CHILDHOOD CANCER


Physiologic Measures of CV Reserve

**VO₂peak**
Product of cardiac output and A-V oxygen difference
Inversely correlated with death from CV disease and all-cause mortality

- Sedentary adult women
- Patients with breast cancer

*J Clin Oncol, 2012, 30: 2530-37*

*Biol Blood Marrow Transplant. 2017 Apr;23(4):700-705*
Blood biomarkers: Clonal Hematopoiesis

- We accumulate somatic mutations in blood with age
- Common mutations: (DNMT3, TET2, ASXL1, JAK2)
- Increased in risk
  - Hematologic cancer (HR 11.1)
  - All-cause mortality (HR 1.4)
  - Incident coronary heart disease (HR 2.0)
  - Ischemic stroke (HR 2.6)
Clonal Hematopoiesis
Clonal Hematopoiesis in Hematology Patients

Clonal Hematopoiesis Associated With Adverse Outcomes After Autologous Stem-Cell Transplantation for Lymphoma

J Clin Oncol 35. © 2017

A
Cumulative Incidence of TMN

B
Overall Survival

Increased local cytokine production may drive atherosclerotic and/or thrombotic processes that promote end-organ damage

Nonmutated cells
Cells with 1 mutation
Cells with 2 mutations
Cells with 3 mutations

Common mutations
DNMT3A
Tet2
ASXL1
JAK2

Tissue mononuclear phagocyte bearing CHIP mutation

Acute leukemia
Pulmonary embolism
Ischemic stroke
Myocardial infarction

Clonal Hematopoiesis and CVD

Somatic Tet2 mutations within hematopoietic stem and progenitor cells (HSPC) will lead to their clonal amplification. These HSPC give rise to myeloid cell progeny that promote cardiac remodeling through excessive production of interleukin-1β (IL-1β).
CV Risk Factor Management

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group®

Hazard ratio with intensive treatment, 0.75 (95% CI, 0.64–0.89)

Standard treatment

Intensive treatment

N Engl J Med 373;22  NEJM.org  November 26, 2015
CV Risk Factors and Heart Failure: *HCT Survivors*

Model adjusted for: Sex, Diagnosis, Pre-Tx CV Risk Factor

- Thyroid
- Dyslipidemia
- Diabetes
- Hypertension

† p<0.05

*Blood, 2011, 118: 6023-9*
CV Risk Factor Management

J Clin Oncol 32. © 2014
Challenges to Long-Term CVD Prevention

% Utilization

Years since transplant

Cancer Epidemiol Biomarkers Prev 2007; 16(4): 834

M-Health to Optimize Cardio-Oncology Care

Algorithm-based remote monitoring and management of CVRFs
Take home messages

• Growing number of survivors at risk for developing CVD during and after therapy
  – Late effects of hematologic cancer treatment a reality, but not a fatality
  – The occurrence of late effects and well-being not a contradiction

• Longitudinal studies needed to characterize CVD in hematology patients
  – Phenotype, Biomarkers, Genetics
  – Early screening and detection of chronic health conditions

• Evidence-based guidelines: cost-effectiveness of recommendations

• New paradigms in care delivery needed for the changing healthcare landscape

• Collaborative efforts to translate observational studies into prevention research
  – Continued dialogue with primary care providers and subspecialists
  – Integrated curriculum for the next generation of care providers