Epidemiology of Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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Outline

• Burden of Disease
• Etiology:
  – Focus: factors that influence an individual’s risk to develop a disease
  – Implication: primary prevention
• Health Outcomes:
  – Focus: factors that affect identification of disease or prognosis after disease develops
  – Implication: secondary & tertiary prevention
Burden of Disease
Characterization of MDS and MPN

• In 2000, in the International Classification of Diseases for Oncology, 3rd edition (ICDO-3), the behavior code of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) changed from “1 (uncertain/borderline)” to “3 (malignant)”.

• In 2001, MDS and MPN became reportable to cancer registries, such as the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

Age-Standardized Incidence Rate of MDS By Sex and Year of Diagnosis: SEER, 2001-2012

Incidences:
- Overall: 4.7/100,000
- Male: 6.3/100,000
- Female: 3.6/100,000

Total # of patients: ~44,500
MDS Incidence Rate By Age: SEER, 2001-2012

Median age at diagnosis:
76 years
# of New MDS Cases in the US Annually

- Estimates vary substantially
  - **1,500**: a book published in 1995 \(^1\)
  - ~ **10,000**: two cancer registry-based studies published in 2007 and 2008 \(^2,3\)
  - > **40,000**: a 2010 study based on Medicare claims \(^4\)

- Registries such as SEER are usually considered an authoritative source for cancer incidence, but MDS is a challenging disease.

Probable Under-reporting by Cancer Registries

- Registries typically rely on inpatient surveillance for cancer incidence, but MDS is commonly diagnosed and managed outside the hospital setting.\(^1\)
  - During 2001-2009, SEER guidelines only required capture of the first myeloid malignancy.
- The extent to which MDS is under-reported is unclear.

Studies Addressing Under-reporting

• A study using claims-based algorithms reported an annual incidence of 75 per 100,000 in persons ≥65 years, more than 3 times the SEER estimate. ¹

• By reviewing electronic pathology reports, another study found that only two-thirds of true MDS cases were captured by the Florida Cancer Registry using current case-finding mechanisms. ²

Prevalence of MDS

- Estimated prevalence of 20.7/100,000 in Germany
  - Translates to 60,000 people in the US?
  - Likely an underestimate due to failure to diagnose

- 945,000 individuals aged ≥ 65 years in the US had unexplained anemia as of 1990-1994, and MDS may be a more precise diagnosis for many of them.

References:
Observed Survival by Sex: SEER, 2001-2012

Median survival: 25 months
Agents Approved for the Treatment of MDS by the US Food and Drug Administration

- Azacitidine: May 2004
- Lenalidomide: December 2005
- Decitabine: May 2006
SEER: Survival of MDS Patients by Year of Diagnosis

Survival probability

Years since MDS diagnosis

- 2001-2003
- 2007-2010

Log-rank p=0.08
SEER: Survival of Refractory Anemia with Excess Blasts (RAEB) Patients by Year of Diagnosis

Log-rank p=0.01
Age-Standardized Incidence Rate of MPN
By Sex and Year of Diagnosis: SEER, 2001-2013
Under-reporting of MPN by Cancer Registries (likely more severe than that of MDS)

- Substantial discrepancy in incidence rate of PV during 2001-2003 based on **SEER records** and **Medicare claims**
  - SEER-reported incidence rate: 3.5 – 4.1 per 100,000
  - Estimates from Medicare claims: 13.1 – 14.4 per 100,000

Prevalence of MPN in the United States

• By using health claims data from insurance payers and conducting a validation study with patient chart review, we estimated the # of MPN patients residing in the US as of 2003: ¹
  – PV: 65,243
  – ET: 71,078

• Unable to estimate prevalence of myelofibrosis due to small sample size

Etiology of MDS and MPN
Risk Factors for MDS

• Chemotherapy and/or radiotherapy for previous cancer
• Exposure to benzene
• Tobacco smoking
• Other possible risk factors: obesity, infection

History of Radiotherapy and MDS

- The literature is fairly consistent that radiotherapy for a previous cancer is a risk factor for MDS.

- A retrospective cohort study of 10,924 prostate cancer patients diagnosed during 1986-2011 at Cleveland Clinic found that patients who received radiotherapy and those who underwent surgery had a similar incidence of subsequent MDS, with a median follow up of 3 years.\(^1\)

## Influence of Lifestyle Factors on MDS Risk

<table>
<thead>
<tr>
<th>Lifestyle Factor</th>
<th># of Cases</th>
<th>Person-yrs of follow-up</th>
<th>Hazard Ratio (95% CI)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cigarette Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Never</td>
<td>42</td>
<td>1,215,608</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Quit, ≤1 pack/day</td>
<td>56</td>
<td>954,835</td>
<td>1.55 (1.04-2.32)</td>
<td></td>
</tr>
<tr>
<td>Quit, &gt;1 pack/day</td>
<td>53</td>
<td>724,524</td>
<td>1.87 (1.23-2.83)</td>
<td></td>
</tr>
<tr>
<td>Current, ≤1 pack/day</td>
<td>18</td>
<td>252,160</td>
<td>2.42 (1.39-4.21)</td>
<td></td>
</tr>
<tr>
<td>Current, &gt;1 pack/day</td>
<td>18</td>
<td>135,193</td>
<td>4.70 (2.68-8.24)</td>
<td></td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>18.5 ≤ BMI &lt; 25</td>
<td>51</td>
<td>1,191,019</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>25 ≤ BMI &lt; 30</td>
<td>78</td>
<td>1,476,192</td>
<td>1.15 (0.81-1.64)</td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>64</td>
<td>740,187</td>
<td>2.18 (1.51-3.17)</td>
<td></td>
</tr>
</tbody>
</table>

Data from the NIH-AARP Diet and Health Study, 1995 - 2003. Cohort of 600,000 50-71 year olds.

Spatial-Temporal Clustering in the Incidence of MDS in Connecticut

* The area included 46 census tracts and more than 214,000 individuals. Over the three-year period, there were 41 MDS cases, while the expected number was 14. O/E ratio = 2.8, p = 0.0001.

A Possible Etiologic Role for Obesity and Other Factors

- Association between obesity and MDS persisted in males and females, smokers and non-smokers, and individuals with different levels of physical activity. ¹

- Spatial and space-time clustering of MDS may be consistent with hypotheses regarding infection and/or environmental chemicals. ²

- We are currently assessing exposure to traffic as a possible risk factor for MDS (R01 CA169043, PI: Ma & Guan).

Risk Factors for MPN

- Family history
- Exposure to benzene
- Other possible risk factors: tobacco smoking, history of autoimmune disease
- Very few existing studies
Some Recent Observations

• In the prospective Iowa Women’s Health Study cohort (n=27,370), 172 ET patients and 64 PV patients were identified.

• Risk factor profiles were mostly distinct for ET and PV. ¹
  – ET: energy balance factors, e.g., obesity, physical activity, adult onset diabetes; aspirin use
  – PV: current smoking

Health Outcomes Research
Factors Influencing MDS Survival

- Older age, male gender, high blast %, # of cytopenias, transfusion dependence, and certain cytogenetic characteristics have been linked to poor survival.

- Additional patient characteristics indicated
  - Comorbid conditions
  - Socioeconomic status
## Prevalence of Comorbidities in MDS Patients

<table>
<thead>
<tr>
<th>Comorbid Conditions</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>21.1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>20.7</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>18.6</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8.2</td>
</tr>
<tr>
<td>Peripheral vascular disease (diagnosis)</td>
<td>7.0</td>
</tr>
<tr>
<td>Diabetes w/ sequelae</td>
<td>5.6</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>5.6</td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>4.4</td>
</tr>
<tr>
<td>Rheumatoid diseases</td>
<td>3.5</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.0</td>
</tr>
<tr>
<td>Acute ulcers</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Data from SEER-Medicare database: incident MDS cases reported to SEER, ≥66 years

## Adjusted Hazard Ratios of Death

<table>
<thead>
<tr>
<th>Median Household Income</th>
<th>Hazard Ratio (95% CI)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; quartile</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; quartile</td>
<td>1.03 (0.89-1.18)</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; quartile</td>
<td>0.87 (0.75-1.01)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; quartile</td>
<td>0.82 (0.70-0.95)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Charlson Comorbidity Index</th>
<th>Hazard Ratio (95% CI)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>1.16 (1.04-1.30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 3</td>
<td>1.73 (1.51-1.99)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Comorbidity and Survival in MDS

Comorbid Conditions | HR* | 95% CI
--- | --- | ---
Congestive heart failure | 1.35 | 1.16-1.57
Cerebrovascular disease | 1.02 | 0.82-1.27
Chronic obstructive pulmonary disease | 1.36 | 1.16-1.58
Diabetes | 1.09 | 0.93-1.28

*Adjusted for age, sex, median household income, MDS subtype and other comorbidities.

Additional Studies of Comorbidities in MDS

- Hematopoietic stem-cell transplant-specific comorbidity index vs. Charlson comorbidity index in Austrian patients (n = 419) \(^1\)
- Development and validation of MDS-specific comorbidity index in German patients (n = 1,344) \(^2\)
- Application of MDS-specific comorbidity index to identify patients who have a greater chance of benefiting from azacitidine in Italy (n = 60) \(^3\)

Cost of Care for Elderly MDS Patients

- Among 6,556 MDS patients ≥ 66.5 years, the expected MDS-related 5-year cost was $63,223 (95% CI: $59,868–66,432 in 2009 dollars), higher than any of the 18 most prevalent cancers in the US. ¹

- Medicare expenditure for elderly MDS patients varied considerably across SEER registries but was not associated with 2-year survival. ²

Health Outcomes of MPN Patients

• 3-year relative survival of MPN as a group: 80%  

• Median survival in an Italian patient cohort was 20 years for PV and 22.6 years for ET.  

• In a SEER-Medicare population, MPN patients had significantly worse median survival than matched non-cancer “controls”.  

  – **PV**: 65 vs. 104 months  
  – **ET**: 68 vs. 101 months  
  – **MF**: 24 vs. 106 months

Impact of MPN on Health and Productivity

• Of 813 MPN patients under active management in the US (PV: 380, ET: 226, MF: 207), many had experienced MPN-related symptoms ≥ 1 year before diagnosis (PV: 61%, ET: 58%, MF: 49%).

• Many respondents, even those with low prognostic risk scores, reported reduced quality of life, reductions in activities of daily living, and lower work productivity.

Summary

• MDS and MPN are understudied, and the disease burden will continue to increase.

• The etiology of both is not well understood.

• While newer treatments are available for MDS and MPN, the impact of these regimens remains to be evaluated.
Acknowledgement

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