Institute of Medicine

2013 National Cancer Policy Summit

New Opportunities and Challenges in Cancer Research and Care

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Cutting the Gordian Knot
a bold solution to a complicated problem

- 333 BCE Alexander the Great was shown chariot of ancient founder of Gordius, its yoke lashed to pole by means of an intricate knot.
- Knot was to be **untied** only by future conqueror of Asia.
- Unable to locate ends of knot, Alexander sliced through knot with his sword.
- The phrase “cutting the Gordian knot” has thus come to denote a **bold solution to a complicated problem**.

Better to have prevented the knot from being tied in the first place.
Overview

• **Background**
  – Despite substantial progress, most established cancers are relatively impervious to treatment
  – Chemotherapy, radiation, and immunotherapy are our “swords”
    • Targeted therapies our “daggers”

• **Prediction**
  – Improved diagnostics and informatics will allow robust prediction of cancer susceptibilities and identification of pre-malignancies (“cancer susceptibility disorders”)

• **Impact**
  – Evolution from “diseasecare” to healthcare
From Susceptibility to Malignancy

![Diagram showing stages of cancer development]

- **NORMAL** to **INITIATED**
- **MILD**, **MODERATE**, **SEVERE**, **CIS** to **CANCER**

<table>
<thead>
<tr>
<th>Location</th>
<th>Initiation Time</th>
<th>Pre-Cancer Stage</th>
<th>Development Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5–20 years</td>
<td>Adenoma</td>
<td>5–15 years</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Tobacco use</td>
<td>Dysplastic oral leukoplakia</td>
<td>6–8 years</td>
</tr>
<tr>
<td>Cervix</td>
<td>CIN 1</td>
<td>9–13 years</td>
<td>CIN 3/CIS 10–20 years</td>
</tr>
<tr>
<td>Lung (smokers)</td>
<td>Atypical hyperplasia</td>
<td>20–40 pack-years</td>
<td>DCIS 6–10 years</td>
</tr>
<tr>
<td>Breast</td>
<td>PIN</td>
<td>≥10 years</td>
<td>Latent cancer 3–15 years</td>
</tr>
</tbody>
</table>
Chronic Myelogenous Leukemia

Response to Imatinib

(A) chronic phase
(B) accelerated phase
(C) blast crisis
Treatment of Smoldering Myeloma

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

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Smoldering Myeloma

• **Background**
  – Predictable progression to fatal myeloma
  – Observation is standard of care

• **Methods**
  – Randomized 119 high-risk patients to Rx vs. observation.
  – Induction
    • lenalidomide 25 mg/d, x 21d, plus dex 20 mg/day, d 1 to 4 and d 12 to 15, at 4-week intervals x 9 cycles
  – Maintenance
    • lenalidomide 10 mg/day d 1 to 21 of each 28-day cycle for 2 years
  – Primary end point
    • TTP to symptomatic disease.
  – Secondary end points
    • response rate, overall survival, and safety.

(Funded by Celgene; ClinicalTrials.gov number, NCT00480363.)

• **Results**
  – TTP > in Rx group (median not reached vs. 21 months; HR 0.18; 95% confidence interval [CI], 0.09 to 0.32; P<0.001).
  – 3-year OS Rx group 94% vs. 80%; HR, 0.31; 95% CI, 0.10 to 0.91; P = 0.03).
  – OS from time of Dx SMM at 5 years, 94% vs. 78% in the observation group; HR 0.28; 95% CI, 0.09 to 0.91; P = 0.02)
  – Toxic effects mainly grade 2 or lower.

(Funded by Celgene; ClinicalTrials.gov number, NCT00480363.)
Policy Implications

• Develop policies that:

1. Promote increased understanding of the basis for and diagnosis of genotypic susceptibility to phenotypic progression of disease

2. Help identify and validate surrogate endpoints of clinical benefit

3. Shape regulatory environment to encourage early intervention