Malignant Melanoma and NMSC in the setting of CLL

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Disclosures

• None
The Dermatology Foundation has supported & advanced my career.
Objectives

- Immunosuppression and Malignancy
  - Introduction
  - Pathogenesis
  - Epidemiology
  - Outcomes
  - Conclusions
I have seen bad outcomes in patients with lymphoma and skin cancer in my practice…

1. Frequently
2. Fairly regularly
3. Rarely
4. Never
Introduction
Skin Cancer

- Most common human malignancy
- 3-5 million NMSC per year in US
- Increased incidence and risk
  - Solid organ transplantation
  - NHL/CLL
Common Susceptibility
NMSC and NHL as 2nd Primary Cancers

- NMSC and NHL
  - Each are the most common second primary cancers after the development of the first

Risk of CLL in Cancer Survivors

- Netherlands Cancer Registry
  - 1,313,232 cancer survivors
- Risk of developing CLL
  - 90% higher than general population
  - Within the 1st year
    - SIR 4.4 (4.1-4.8)

Organ Transplantation
Organ Transplantation

• Final defect size
  • 8.1x5.5cm
Lymphoma
Lymphoma
Lymphoma

• 4 months later
Non-Hodgkins Lymphoma
Chronic Lymphocytic Leukemia

• NHL is 7th most common malignancy
• CLL is a form of NHL
  • Low grade B-cell malignancy
  • 25% of all leukemias
  • Incidence tripled – 1958 to 1992
Cancer 2015

Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>220,800</td>
<td>231,840</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>115,610</td>
<td>105,590</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>69,090</td>
<td>63,610</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>56,320</td>
<td>54,870</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>42,670</td>
<td>47,230</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>39,850</td>
<td>32,000</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>38,270</td>
<td>31,200</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>32,670</td>
<td>24,120</td>
</tr>
<tr>
<td>Leukemia</td>
<td>30,900</td>
<td>23,370</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>25,510</td>
<td>23,290</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>848,200</strong></td>
<td><strong>810,170</strong></td>
</tr>
</tbody>
</table>

Pathogenesis
Skin Cancer in Immunosuppressed Patients

• Multiple theories
  • Direct carcinogenesis from medications
  • Increased infections
    • Human papilloma virus
  • Common underlying mutations
  • Dysfunctional lymphocytes
    • Impaired immune surveillance
    • Impaired cytotoxic functions
Epidemiology
Epidemiology of Skin Cancer in Patients with Immunosuppression

- In patients with NHL/CLL
  - NMSC: ↑ 2.4 to 8.1 fold
  - SCC: ↑ 5.0 to 8.6 fold
  - BCC: ↑ 2.7 to 3.6 fold
  - MM: ↑ 2.1 to 6.7 fold

- In OTRs
  - ↑ 25 fold
  - ↑ 65 fold
  - ↑ 10 fold
  - ↑ 2 to 8 fold
Incidence of Skin Cancer in CLL (SIR’s)

- Melanoma
  - 2.3 (95% CI – 2.0 - 2.7)
- Merkel cell carcinoma
  - 8.2 (95% CI – 5.6 - 11.6)
- MFH
  - 3.6 (95% CI – 2.1 -6.0)
- DFSP
  - 2.5 (95% CI – 0.3 - 9.0)
- Kaposi's sarcoma
  - 2.9 (95% CI – 1.0 - 6.2)
- Sebaceous carcinoma
  - 1.4 (95% CI – 0.7 - 2.4)

Increased Incidence of Skin Cancer in the setting of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; a SEER and Rochester Epidemiology Project Population Based Study

Brewer, JD, Shanafelt TG, Khezri, F, Call TG, Roenigk RK, Smith CY, Weaver AL, Otley, CC.

Increased Incidence of Skin Cancer in the setting of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; a SEER and Rochester Epidemiology Project Population Based Study. (data prior to submission)
Study Sample

- 558 Olmsted County residents
  - Diagnosed with lymphoma 1976 to 2005
  - 261 CLL/SLL (46.8%)
  - 297 NHL (53.2%)
- Followed until death or last follow-up
- Up to 34 years of follow-up
  - Mean follow-up 7.7 years

Brewer JD, Shanafelt TD, Khezri F, Call TG, Roenigk RK, Smith CY, Weaver AL, Otley CC. Increased Incidence of Skin Cancer in the setting of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; a SEER and Rochester Epidemiology Project Population Based Study. 2012. Data prior to submission.
NMSC Following Lymphoma

- 520 patients
  - No prior BCC
  - 250 (48.1%) CLL
  - 270 (51.9%) NHL
- 67 patients
  - 175 BCCs

- 522 patients
  - No prior SCC
  - 249 (47.7%) CLL
  - 273 (52.3%) NHL
- 87 patients
  - 241 SCCs

- SCC to BCC Ratio of 1.4:1

Brewer JD, Shanafelt TD, Khezri F, Call TG, Roenigk RK, Smith CY, Weaver AL, Otley CC. Increased Incidence of Skin Cancer in the setting of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; a SEER and Rochester Epidemiology Project Population Based Study. 2012. Data prior to submission.
Incidence of Skin Cancer after Lymphoma

• BCC in CLL/NHL patients
  • At 10 years
    • 18.2% (95% CI – 13.4, 22.7)
  • At 20 years
    • 25.6% (95% CI – 18.6, 31.9)

• SCC in CLL/NHL patients
  • At 10 years
    • 20.6% (95% CI – 15.6, 25.2)
  • At 20 years
    • 40.3% (95% CI – 29.8, 49.2)

Brewer JD, Shanafelt TD, Khezri F, Call TG, Roenigk RK, Smith CY, Weaver AL, Otley CC. Increased Incidence of Skin Cancer in the setting of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; a SEER and Rochester Epidemiology Project Population Based Study. 2012. Data prior to submission.
Incidence of First BCC/SCC after Lymphoma

Brewer JD, Shanafelt TD, Khezri F, Call TG, Roenigk RK, Smith CY, Weaver AL, Otley CC. Increased Incidence of Skin Cancer in the setting of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; a SEER and Rochester Epidemiology Project Population Based Study. 2012. Data prior to submission.
Incidence of Skin Cancer after CLL

- **BCC in CLL patients**
  - At 10 years
    - 21.3% (95 CI – 13.9, 28.1)
  - At 20 years
    - **30.9% (95% CI – 19.3, 40.9)**

- **SCC in CLL patients**
  - At 10 years
    - 23.5% (95 CI – 15.9, 30.5)
  - At 20 years
    - **45.2% (95% CI – 29.3, 57.5)**

Brewer JD, Shanafelt TD, Khezri F, Call TG, Roenigk RK, Smith CY, Weaver AL, Otley CC. Increased Incidence of Skin Cancer in the setting of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; a SEER and Rochester Epidemiology Project Population Based Study. 2012. Data prior to submission.
Outcomes
BCC and SCC
BCC and CLL

- 24 patients with BCC and CLL
- 66 matched controls
- Mohs micrographic surgery
- 22% 5-year local recurrence rate
  - p=0.016, 95% CI 1.6-115.1, RR 13.7

SCC and CLL

- 28 patients with SCC and CLL
- 114 matched controls
- Mohs micrographic surgery
- 19% 5-year local recurrence rate
  - p=0.003, 95% CI 2.0-25.3, RR 7.1

SCC and CLL
Metastatic Potential

- 28 patients with CLL
- 56 matched controls
- 19% 5-year metastatic rate (p=0.0031)
- All mets to regional nodes
- In transit metastasis also occurred
- 11% death rate (p=0.0033)

Recurrence

• Rochester Epidemiology Project
  • 717 patients (282 with CLL, 435 with NHL)

• BCC
  • Recurrence rate post excision surgery
    • 7.6% at 5 years
  • Recurrence rate post Mohs surgery
    • 8.3% at 8 years

• SCC
  • Recurrence post excision
    • 10.9% at 5 years
  • Recurrence rate post Mohs surgery
    • 13.4% at 5 years

Metastasis of BCC/SCC

- Only 4 metastases after lymphoma (0.6%)
  - 67 yo female - primary SCC 17.5 years post NHL
    - Metastasized 8 days post diagnosis
    - Died of metastatic SCC 4.5 months later
  - 61 yo male - primary SCC of scalp 7 years post CLL
    - Metastasized 3.5 years post diagnosis
    - Died of metastatic SCC 10.5 months later
  - 80 yo male - primary SCC of neck 14 years post NHL
    - Metastasis to LN noted 3 days post diagnosis
  - 73 yo male – primary SCC of forehead 8 years post CLL
    - Metastasized to parotid and LN 2 years post diagnosis

Summary
Non-Melanoma Skin Cancer and Lymphoma

• Less tumor burden than organ transplant recipients
• High recurrence rate
  • Therapeutic failures after Mohs
  • Especially with SCC
• Rare highly aggressive skin cancer
  • Life threatening
  • Metastasis of NMSC
Melanoma
MM and CLL

• Tashima et al 1973
  • 1st proposed an association with MM and lymphoid neoplasia

• Since then
  • Many large population based studies
    • Have found an increased risk of MM in the setting of lymphoid neoplasia

Melanoma and CLL

- 1990-2006 in the 17 SEER regions
- 212,245 cases with follow-up
- 1,246 had a prior diagnosis
  - 508 CLL (40.8%)
  - 738 NHL (59.2%)
  - Median of 2.7 years prior to MM
  - Diagnosed with MM on average 12 years later
- Relative risk of subsequent MM
  - Pts with CLL - 2.3

Brewer JD, Shanafelt TD, Otley CC, Roenigk RK, Cerhan JR, Kay NE, Weaver AL, Call TG. Chronic Lymphocytic Leukemia is Associated with Decreased Survival of Patients with Malignant Melanoma and Merkel Cell Carcinoma in a SEER Population Based Study. *J Clin Oncol.* 2012;30(8): 843-849.
Overall Survival

Brewer JD, Shanafelt TD, Otley CC, Roenigk RK, Cerhan JR, Kay NE, Weaver AL, Call TG. Chronic Lymphocytic Leukemia is Associated with Decreased Survival of Patients with Malignant Melanoma and Merkel Cell Carcinoma in a SEER Population Based Study. *J Clin Oncol.* 2012;30(8): 843-849.

* Expected survival for patients of the same sex and age derived from melanoma patients without CLL/NHL (N=210,999).
MM Cause-Specific Survival

MCC and CLL

- 1990-2006 in the 17 SEER regions
- 3,613 cases with follow-up
- 90 had a prior diagnosis
  - CLL (n=48)
  - NHL (n=42)
<table>
<thead>
<tr>
<th>Months</th>
<th>Observed (N=48)</th>
<th>Expected* (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>49.1%</td>
<td>61.6%</td>
</tr>
<tr>
<td>24</td>
<td>28.1%</td>
<td>38.2%</td>
</tr>
<tr>
<td>36</td>
<td>23.4%</td>
<td>33.9%</td>
</tr>
</tbody>
</table>

**SMR (95% CI)**

- Prior history of CLL: 3.07 (2.20 - 4.27), p<0.001
- Prior history of NHL: 1.85 (1.24 - 2.78), p=0.002

* Expected survival for patients of the same sex and age derived from MCC patients without CLL/NHL (N=3,523).

Brewer JD, Shanafelt TD, Otley CC, Roenigk RK, Cerhan JR, Kay NE, Weaver AL, Call TG. Chronic Lymphocytic Leukemia is Associated with Decreased Survival of Patients with Malignant Melanoma and Merkel Cell Carcinoma in a SEER Population Based Study. *J Clin Oncol.* 2012;30(8): 843-849.
MCC Cause-Specific Survival

Rare forms of Skin Cancer and CLL/NHL
Rare Cutaneous Tumors and CLL

- 1990-2006 in the 17 SEER regions
  - DFSP ($n=4,184$)
  - MFH ($n=6,334$)
  - KS ($n=10,313$)
  - Sebaceous Ca ($n=4,190$)

- Number with a prior history of CLL/NHL
  - $n=8$
  - $n=78$
  - $n=230$
  - $n=32$

Brewer JD, Shanafelt TD, Call TG, Roenigk RK, Weaver AL, Otley CC. Dermatofibrosarcoma Protuberans, Malignant Fibrous Histiocytoma, Kaposi’s Sarcoma and Sebaceous Carcinoma in patients with Chronic Lymphocytic Leukemia: a SEER Population Based Study. 2015 (data prior to print).
DFSP

- Only 8 with a prior history of CLL/NHL
- 5 dead at last follow-up
  - None due to DFSP
- More studies needed

Brewer JD, Shanafelt TD, Call TG, Roenigk RK, Weaver AL, Otley CC. Dermatofibrosarcoma Protuberans, Malignant Fibrous Histiocytoma, Kaposi’s Sarcoma and Sebaceous Carcinoma in patients with Chronic Lymphocytic Leukemia: a SEER Population Based Study. 2015 (data prior to print).
## MFH – Overall Survival

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Overall survival</th>
<th>SMR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 yr</td>
<td>2 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>CLL (N=35)</td>
<td>78.4%</td>
<td>58.3%</td>
<td>29.9%</td>
</tr>
<tr>
<td>Expected</td>
<td>85.9%</td>
<td>73.6%</td>
<td>45.6%</td>
</tr>
<tr>
<td>NHL (N=43)</td>
<td>78.2%</td>
<td>51.6%</td>
<td>28.3%</td>
</tr>
<tr>
<td>Expected</td>
<td>86.5%</td>
<td>74.5%</td>
<td>46.9%</td>
</tr>
</tbody>
</table>
### MFH – Cause-Specific Survival

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Cause-specific survival</th>
<th>SMR (95 % CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 yr</td>
<td>2 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>CLL (N=35)</td>
<td>83.3%</td>
<td>79.1%</td>
<td>79.1%</td>
</tr>
<tr>
<td>Expected</td>
<td>93.1%</td>
<td>86.6%</td>
<td>69.8%</td>
</tr>
<tr>
<td>NHL (N=43)</td>
<td>97.1%</td>
<td>93.6%</td>
<td>75.4%</td>
</tr>
<tr>
<td>Expected</td>
<td>93.3%</td>
<td>87.2%</td>
<td>70.6%</td>
</tr>
</tbody>
</table>
## KS – Overall Survival

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Overall survival</th>
<th>SMR (95 % CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 mo</td>
<td>1 yr</td>
<td>2 yrs</td>
</tr>
<tr>
<td>CLL (N=10)</td>
<td>57.1%</td>
<td>57.1%</td>
<td>45.7%</td>
</tr>
<tr>
<td>Expected</td>
<td>94.1%</td>
<td>89.1%</td>
<td>79.6%</td>
</tr>
<tr>
<td>NHL (N=220)</td>
<td>47.5%</td>
<td>31.1%</td>
<td>21.8%</td>
</tr>
<tr>
<td>Expected</td>
<td>89.3%</td>
<td>80.5%</td>
<td>65.8%</td>
</tr>
</tbody>
</table>
## KS – Cause-Specific Survival

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Cause-specific survival</th>
<th>SMR (95 % CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 mo</td>
<td>1 yr</td>
<td>2 yrs</td>
</tr>
<tr>
<td>CLL (N=10)</td>
<td>90.0%</td>
<td>90.0%</td>
<td>72.0%</td>
</tr>
<tr>
<td>Expected</td>
<td>97.9%</td>
<td>96.0%</td>
<td>92.3%</td>
</tr>
<tr>
<td>NHL (N=220)</td>
<td>52.0%</td>
<td>37.2%</td>
<td>28.3%</td>
</tr>
<tr>
<td>Expected</td>
<td>90.7%</td>
<td>83.1%</td>
<td>70.1%</td>
</tr>
</tbody>
</table>
Sebaceous Carcinoma – Overall Survival

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Overall survival</th>
<th>SMR (95 % CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 yr</td>
<td>2 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>CLL (N=11)</td>
<td>100%</td>
<td>100%</td>
<td>75.0%</td>
</tr>
<tr>
<td>Expected</td>
<td>90.8%</td>
<td>82.3%</td>
<td>59.8%</td>
</tr>
<tr>
<td>NHL (N=21)</td>
<td>84.3%</td>
<td>59.9%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Expected</td>
<td>92.8%</td>
<td>85.8%</td>
<td>65.5%</td>
</tr>
</tbody>
</table>
### Sebaceous Carcinoma – Cause-Specific Survival

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>Cause-specific survival</th>
<th>SMR (95 % CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 yr</td>
<td>2 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>CLL (N=11)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Expected</td>
<td>98.1%</td>
<td>96.2%</td>
<td>90.3%</td>
</tr>
<tr>
<td>NHL (N=21)</td>
<td>88.5%</td>
<td>88.5%</td>
<td>78.7%</td>
</tr>
<tr>
<td>Expected</td>
<td>98.3%</td>
<td>86.7%</td>
<td>92.7%</td>
</tr>
</tbody>
</table>

* Unable to estimate since there were no events in the CLL only group

Brewer JD, Shanafelt TD, Call TG, Roenigk RK, Weaver AL, Otley CC. Dermatofibrosarcoma Protuberans, Malignant Fibrous Histiocytoma, Kaposi’s Sarcoma and Sebaceous Carcinoma in patients with Chronic Lymphocytic Leukemia: a SEER Population Based Study. 2015 (data prior to print).
Other Solid Cancers and CLL/NHL
Solid Cancers and CLL

- 1990-2006 in the 17 SEER regions
  - Breast (n=579,164)
  - Colon (n=412,366)
  - Prostate (n=631,616)
  - Lung (n=489,053)
  - Kidney (n=95,795)
  - Pancreas (n=82,116)
  - Ovary (n=61,937)

- Number with a prior history of CLL/SLL
  - n=608
  - n=892
  - n=1257
  - n=1298
  - n=231
  - n=141
  - n=67

## Overall Survival

<table>
<thead>
<tr>
<th>Cancer</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>568,598</td>
<td>1.70</td>
<td>1.51-1.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Colon</td>
<td>394,695</td>
<td>1.65</td>
<td>1.53-1.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney</td>
<td>91,991</td>
<td>1.54</td>
<td>1.29-1.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung</td>
<td>459,256</td>
<td>1.19</td>
<td>1.12-1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovary</td>
<td>58,986</td>
<td>1.04</td>
<td>0.78-1.38</td>
<td>0.81</td>
</tr>
<tr>
<td>Pancreas</td>
<td>73,117</td>
<td>0.97</td>
<td>0.81-1.18</td>
<td>0.78</td>
</tr>
<tr>
<td>Prostate</td>
<td>501,247</td>
<td>1.92</td>
<td>1.73-2.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## Cancer Specific Survival

### Cancer Specific Survival in Patients with CLL/SLL

<table>
<thead>
<tr>
<th>Cancer</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>567,751</td>
<td>1.41</td>
<td>1.11-1.80</td>
<td>0.005</td>
</tr>
<tr>
<td>Colon</td>
<td>393,784</td>
<td>1.64</td>
<td>1.45-1.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney</td>
<td>91,776</td>
<td>1.41</td>
<td>1.05-1.90</td>
<td>0.02</td>
</tr>
<tr>
<td>Lung</td>
<td>458,394</td>
<td>1.13</td>
<td>1.05-1.22</td>
<td>0.002</td>
</tr>
<tr>
<td>Ovary</td>
<td>58,928</td>
<td>0.88</td>
<td>0.62-1.27</td>
<td>0.50</td>
</tr>
<tr>
<td>Prostate</td>
<td>500,126</td>
<td>1.18</td>
<td>0.87-1.60</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Management
Skin Cancer and Non-Hodgkin’s Lymphoma
What We Know

- Increased risk of local recurrence
- Increased risk of regional metastasis
- Increased risk of death
- Worse prognosis of CLL/NHL
- Demands aggressive multimodality treatment
Increased Local Recurrence/Metastasis

- Careful margin examination
- Consider immuno stains
- Consider wide margin after Mohs for permanent section
- Consider
  - Adjuvant radiation
  - Adjuvant chemotherapy
Prevention

- Education
  - Patient
  - Colleagues
  - Sun protection daily
  - Regular self and dermatologist examination
- Aggressive treatment of actinic keratoses
  - Close monitoring for future skin cancer
  - Field treatment of actinically damaged areas
- Vitamin D supplementation
- Consider systemic retinoid chemoprevention
Conclusions
Lymphoma and other Malignancy

- Increased risk of all common forms of skin cancer
- Increased recurrence
- Worse outcomes
  - BCC
  - SCC
  - MM
  - MCC
  - MFH
  - Kaposi’s Sarcoma
  - Sebaceous carcinoma

- Breast
- Colon
- Lung
- Kidney
- Prostate
How to Unlock the Puzzle...

• Immune system
• Other factors
• Something else that affects carcinogenesis
Summary
What We Don’t Know

• Immunosuppressed patients with skin cancer
  • What is the underlying association
  • Does education and prevention effect outcomes
  • What predicts bad behavior
Skin Cancer Screening

- 113 patients with CLL
- 36% had skin cancer screening within 6 months
- 21% of cohort
  - Eventually developed skin cancer