A past personal or family history of malignancy does NOT preclude the use of either immunomodulators or biologics

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Pro: A past personal or family history of malignancy precludes the use of both immunomodulators and biologics

Thomas A. Ullman, MD, FACP
What’s the fuss?

- Fear of the unknown
- Risk of lymphoma with IMM/TNF
- Confusion between risk of cancer in other diseases (like RA) and IBD (where there is no evidence)
- Patient fears - maybe more so if they’ve experienced or seen cancer in a family member

http://www.foodmatters.tv/ Accessed 12/01/11
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• Patient fears - maybe more so if they’ve experienced or seen cancer in a family member
• Doctor fear of prescribing

What are your alternatives?

If you are going to withhold therapy because of an unproven risk of malignancy based on previous personal or family history, what will you treat with?

What would your patient want?
Personal History of Cancer

- Is there evidence that personal history of cancer should prohibit use of immune suppressives or biologics? **NO**
- Timing is important: “history of” means how long since diagnosis, treatment and NED?
- Are all cancers the same? **NO**
  - solid tumors
    - Infection-associated (HPV- cervical)
    - Non-infectious (2011): breast, colon, etc
  - Lymphoma
    - Role of EBV

Family History of Cancer

- Is there evidence that family history of cancer should prohibit use of immune suppressives or biologics? **NO**

- Do patients know their family history?
  
  **NOT as MUCH as WE’D LIKE THEM TO**
What do we know about family history of cancer in IBD?

• Do you obtain one when you interview a patient?
• FH of colorectal cancer is a risk for dysplasia and colorectal cancer in IBD\textsuperscript{1,2}
• A family history (first degree) of hematopoietic malignancy does increase the risk of NHL, HL or B cell lymphoma in patients (not just IBD) (OR = 1.8, 95% CI = 1.2 to 2.5)\textsuperscript{3}

\textsuperscript{1}Askling et al. Gastroenterology. 2001.
Thiopurines: Leukemia

- Not hereditary
- Thiopurines treat leukemia

Thiopurines: Lymphoma

- Risk of lymphoma acknowledged with thiopurines
- Probably EBV-related
  - Post-transplant lymphoproliferative disorder

Thiopurines: Lymphoma

- Swedish population-based case control (1506 cases and 1229 controls)
- Explored exposures as potential confounders of risk of NHL/HL/B cell lymphoma in patients with FH
  - Smoking
  - UV exposures
  - Medications including immunosuppressive drugs (ever/never use of azathioprine, cyclosporine, methotrexate, cyclophosphamide, or chlorambucil) at least 2 years prior to entry
  - Occupational data
- None were significantly associated with increased risk!


Azathioprine is NOT Associated with Solid Tumors in IBD

- UK study 1994 (Connell, Lancet)
  - 755 azathioprine treated IBD patients
  - No increased risk of solid tumors except slight increase in cervical cancer
- UK study 2002 (Fraser, APT)
  - Retrospective study including 2204 patients with IBD; 626 exposed to azathioprine
  - 4.5% of patients developed cancer in BOTH groups
  - No increase in colorectal, bronchial or breast CA
TNF-inhibitors

What does this mean??

[Image]

FDA Announcements Related to Malignancy with TNF-inhibitors

- **November 2011**: 10 year registry of all malignancies that occur in peds and young (<30) patients
- **April 2011**: Safety Review update on HSTCL in adolescents and young adults receiving TNF and thiopurine
- **August 2009**: Conclusion that there is a risk of lymphoma and leukemia and other malignancies with TNF
- **June 2008**: “FDA is investigating the possible association between the use of medicines known as tumor necrosis factor (TNF) blockers and the development of lymphoma and other cancers in children and young adults.”

This is not related to a personal or family history of malignancy!

- **June 2008**: “FDA is investigating the possible association between the use of medicines known as tumor necrosis factor (TNF) blockers and the development of lymphoma and other cancers in children and young adults.”
Anti-TNF Does Not Increase Risk of Solid Tumors* in RA

- 13,000 patients enrolled, 49% received biologics

The table below shows the odds ratios for different types of cancer:

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>All solid tumors</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Colon</td>
<td>0.8 (0.3-1.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.1 (0.7-1.8)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.9 (0.5-1.3)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.5 (0.1-2.6)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.3 (0.9-5.4)</td>
</tr>
<tr>
<td>Non-melanoma skin</td>
<td>1.5 (1.2-1.8)*</td>
</tr>
</tbody>
</table>

This is not related to a personal or family history of malignancy!

Wolfe, Arthritis and Rheumatism 2007;56:2886.
Anti-Integrin Therapies

Melanoma

- 2 cases of melanoma in MS patients receiving anti-α4β1 therapy (natalizumab)
- Concern that α4β1 blockade may prevent adequate tumor surveillance
- *In conclusion, we recommend that natalizumab not be administered to patients with a personal or family history of melanoma or to those with atypical moles or ocular nevi. At the very least, we recommend that alternative therapies be strongly considered in such patients.*

Melanoma- rebuttal

- Meta-analysis of safety data from clinical trials of natalizumab.
  - Incidence of melanoma in natalizumab pts: 3 of 4250 [0.07%]
  - Incidence of melanoma in placebo pts: 2 of 2059 [0.10%]
  - Rates of melanoma followed a similar pattern: 0.419 per 1000 patient-years among persons who received natalizumab versus 0.823 per 1000 patient-years among persons who received placebo.


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- Postmarketing surveillance data as of December 2007 do not indicate an increased risk of melanoma among more than 21,000 patients who received natalizumab (unpublished data).

Current Recommendations of IBD Management Will Prevent Cancer!

AZA and 6MP Do Not Increase the Risk of Colon Cancer in UC

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutter 2004</td>
<td>0.3</td>
<td>0.2-0.9</td>
</tr>
<tr>
<td>Matula 2005</td>
<td>0.9</td>
<td>0.5-1.8</td>
</tr>
<tr>
<td>Velayos 2006</td>
<td>3.0</td>
<td>0.7-13.6</td>
</tr>
<tr>
<td>Rubin 2006</td>
<td>0.3</td>
<td>0.1-0.7</td>
</tr>
<tr>
<td>Beauserie 2008</td>
<td>0.3</td>
<td>0.1-0.9</td>
</tr>
</tbody>
</table>

Rutter M et al. Gastroenterology 2004; 126:451
Velayos F et al, Gastroenterology 2006; 130:1941
Rubin D et al, DDW 2006
Anti-TNFs May Prevent CRC
(or at least it may in mice)

- Mouse model with severe colonic inflammation and multiple colonic tumors
  - Increased TNF-α and TNF-Rp55 receptor expression
- When treated with etanercept → markedly reduced number and size of tumors
- Upregulation of TNF receptor and NF-kappaB
- Anti-TNF (MP6-XT22) reduced # and size of tumors


Cancer Prevention in IBD

- Colorectal cancer surveillance and action based on dysplastic findings
- Control of inflammation/stratification based on inflammation.
- Vaccination against HPV
- Education and monitoring for skin cancers
Summary and Practical Matters

- There is no evidence that a family history of malignancy or a personal history of malignancy, whether hematopoietic or solid, should result in avoidance of existing immunosuppressive or biologic therapies in IBD.

- Timing of immunosuppressive therapy in a patient with a known malignancy is important to avoid complications of immune suppression if cytotoxic therapies are used to treat the malignancy.
  - When in doubt, obtain additional opinions from oncology.

- Screening and prevention: cervix, skin, colorectum, HPV vaccine

- Must weigh the known and unknown risks of therapeutic exposures with the available treatment options and patient wishes!